VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below:

That I am knowledgeable in the English language and in the language in which the below identified application was filed, and that I believe the English translation of the Japanese Patent Application No. 47037/2004 is a true and complete translation of the above-identified Japanese Patent Application as filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated this 15th day of December, 2009

Full name of the translator Takumi TERACHI

Signature of the translator Takumi Terachi

Post Office Address c/o YUASA AND HARA, Section 206, New Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo, JAPAN

[Name of Document] Patent Application

[Case No] 040227

[Filing Date] February 23, 2004

[To] Commissioner, Patent Office

[International Patent Classification]

C07D

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Nobuhiro OIKAWA

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Eisaku MIZUGUCHI

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Kenji MORIKAMI

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Nobuo SHIMMA

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Nobuya ISHII

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Toshiyuki TSUKAGUCHI

[Applicant for Patent]

[Identification No.] 000003311

[Appellation] CHUGAI SEIYAKU KABUSHIKI KAISHA

[Proxy]

[Identification No.] 100089705

[Address] YUASA AND HARA, Section 206, New Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo

[Patent Attorney]

[Name] Ichio SHAMOTO

[Telephone] 03-3270-6641

[Facsimile] 03-3246-0233

[Proxy]

[Identification No.] 100076691

[Patent Attorney]

[Name] Chuji MASUI

[Proxy]

[Identification No.] 100075270

[Patent Attorney]

[Name] Yasushi KOBAYASHI

[Proxy]

[Identification No.] 100080137

[Patent Attorney]

[Name] Akio CHIBA

[Proxy]

[Identification No.] 100096013

[Patent Attorney]

[Name] Hiroyuki TOMITA

[Fees]

[Page No. of Books] 051806

[Amount] ¥21,000.-

[List of the Documents]

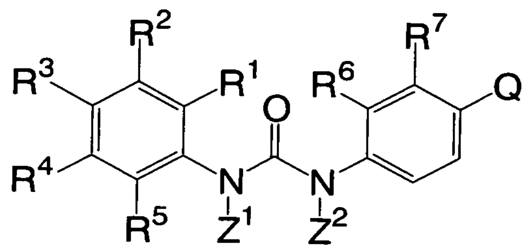
[Item]	Claims	1
[Item]	Specification	1
[Item]	Abstract	1
[General Power of Attorney No.]		0107764

[Name of Document] Claims

[Claim 1]

A compound represented by formula (1):

[Formula 1]



(1)

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group which may be substituted with one or more halogen atoms and a C_1-C_6 alkoxy group which may be substituted with one or more halogen atoms;

R^6 and R^7 are each independently selected from a hydrogen atom and a halogen atom;

Z^1 and Z^2 are each independently selected from a hydrogen atom, a hydroxyl group and $-O(CHR^{11})OC(=O)R^{12}$;

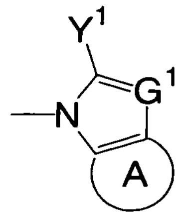
wherein

R^{11} is a hydrogen atom or a C_1-C_6 alkyl group; and

R^{12} is a pyrrolidinyl group, a piperidinyl group, a morpholinyl group, a piperazinyl group, an amino C_1-C_6 alkyl group, a mono- or di(C_1-C_6 alkyl)amino C_1-C_6 alkyl group, an amino C_1-C_6 alkylamino group or a mono- or di(C_1-C_6 alkyl)-amino C_1-C_6 alkylamino group;

Q is a group of the formula:

[Formula 2]



wherein

G^1 is C-Y^2 or N;

ring A is a benzene ring or a 5- to 6-membered unsaturated heterocycle; a nitrogen atom present in the heterocycle may be an N-oxide; and the ring A may be substituted with one to three same or different substituents W;

Y^1 and Y^2 are each independently selected from a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxy C_1-C_6 alkyl group, a C_1-C_6 alkoxy C_1-C_6 alkoxy group, an amino C_1-C_6 alkoxy group, a (C_1-C_6 alkyl)amino C_1-C_6 alkyl group, an amino group, a (C_1-C_6 alkyl)amino group and a di(C_1-C_6 alkyl)amino group;

W is a halogen atom, a nitro group, a cyano group, a hydroxyl group, -NRaRb, -N=C(-Rc)NRaRb, -CONRaRb, -OC(=O)NRaRb, -SO_2NRaRb, -N(-Ra)C(=O)NRa'Rb', -N(-Ra)C(=O)ORd, -N[C(=O)ORd][C(=O)ORd'], -C(=O)ORd, -S(=O)$_m$-Rd, -O-Rd, -OC(=O)Rc, -N(-Ra)C(=O)Rc, -N[C(=O)Rc][C(=O)Rc'], -N(-Ra)SO_2Rc, -N(SO_2Rc)(SO_2Rc'), -C(=NORd)NRa'Rb', -C(=NRa)NRa'Rb', -C(=NORa)Rc, -C(=O)Rc, a C_1-C_6 alkyl group which may be substituted with one or more Y^3,

a C_2-C_7 alkenyl group which may be substituted with one or more Y^3, a C_2-C_7 alkynyl group which may be substituted with one or more Y^3, an aryl group which may be substituted with one or more Y^3 or a heteroaryl group which may be substituted with one or more Y^3;

Ra, Ra', Rb, Rb', Rc, Rc', Rd and Rd' are each independently selected from a hydrogen atom, a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, -[(C_1-C_6 alkylene)-O]$_n$-(C_1-C_3 alkyl), an aryl group or a heteroaryl group, a pyrrolidinyl group and a pyperidinyl group (wherein the pyrrolidinyl group or the pyperidinyl group may be substituted with a C_1-C_3 alkyl group); or

Ra and Rb, Ra' and Rb', Ra and Rd, Ra and Ra', Ra and Rc, Rc and Rc' or Rd and Ra' may form a saturated or unsaturated 5- to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

Ra, Rb, Ra', Rb', Rc, Rc', Rd and Rd' each may be substituted with one to three same or different substituents selected from Y^3;

m is an integer selected from 0 to 2;

n is an integer selected from 1 to 4;

Y^3 is a halogen atom, -NRxRy, -C(=O)ORz, -ORz, -CONRxRy, -OC(=O)NRxRY, -SO_2NRxRy, -N(-Rx)C(=O)NRx'Ry', -N(-Rx)C(=O)ORz, -S-Rz,

-SO-Rz, $-SO_2$-Rz, -OC(=O)Rz, -N(Rx)C(=O)Rz,

-C(=NORz)NRx'Ry', -C(=NRx)NRx'Ry', -C(=NORx)Rz,

-[O-(C_1-C_6 alkylene)]$_n$-O(C_1-C_3 alkyl), -N(-Rx)-(C_1-C_6 alkylene)-O(C_1-C_3 alkyl), -CORz, a C_1-C_6 alkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, an aryl group or a heteroaryl group;

Rx, Rx', Ry, Ry' and Rz are each independently selected from a hydrogen atom and a C_1-C_4 alkyl group;

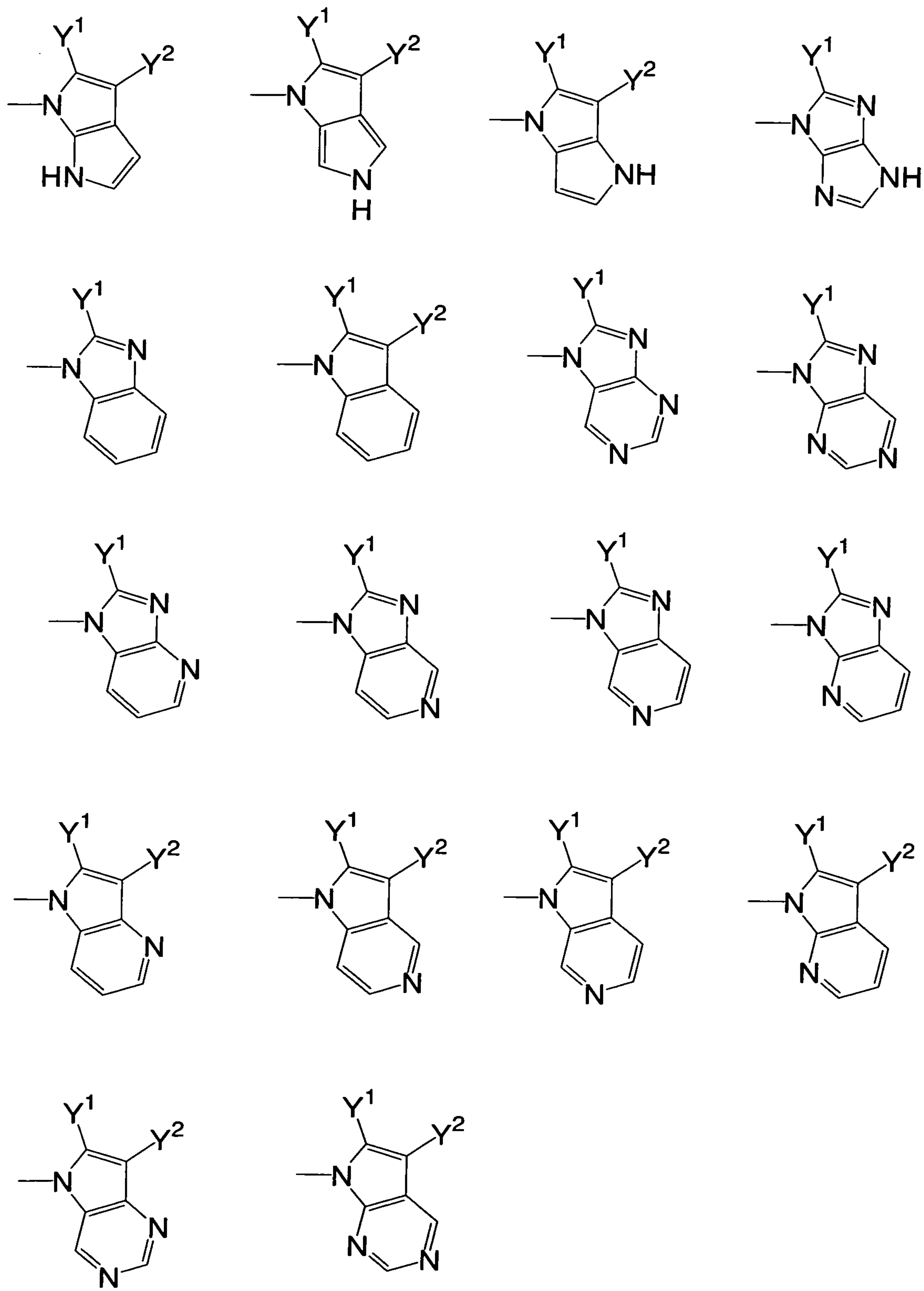
Rx and Ry, Rx and Rx', Rx and Rz or Rz and Rx' may form a saturated or unsaturated 5-to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

a pharmaceutically acceptable salt thereof or a prodrug thereof.

[Claim 2]

The compound of claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein Q is a group of the formula selected from:

[Formula 3]



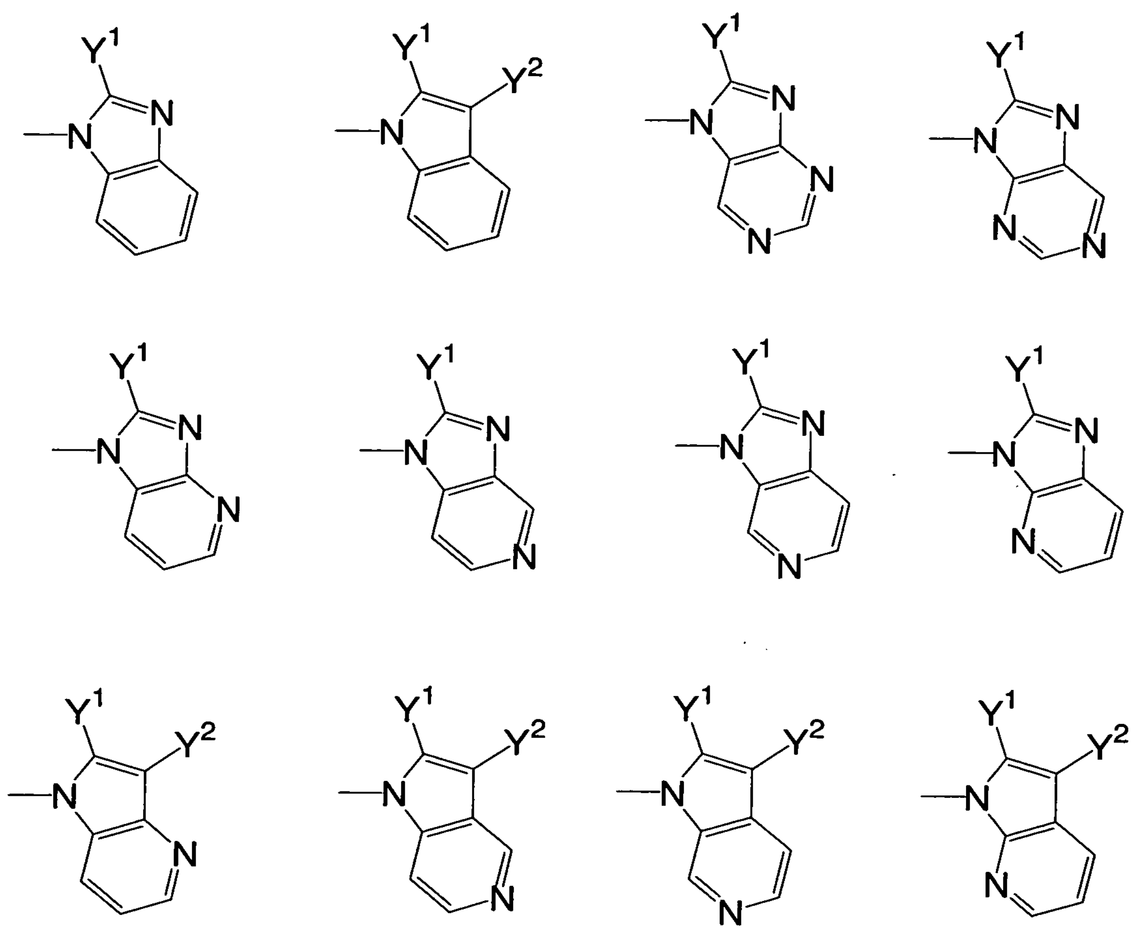
which may be substituted with one to three same or

different substituents W.

[Claim 3]

The compound of claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein Q is a group of the formula selected from:

[Formula 4]

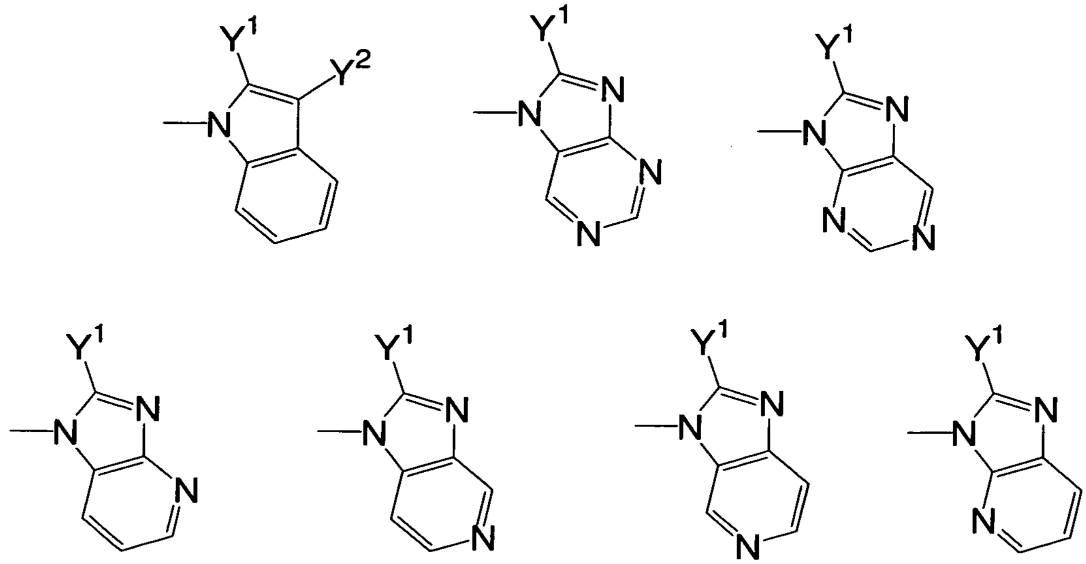


which may be substituted with one to three same or different substituents W.

[Claim 4]

The compound of claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein Q is a group of the formula selected from:

[Formula 5]



which may be substituted with one to three same or different substituents W.

[Claim 5]

The compound of any one of claims 1 to 4, a pharmaceutically acceptable salt thereof or a prodrug thereof,

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a chlorine atom, a fluorine atom, a bromine atom and a trifluoromethyl group;

R^6 and R^7 are hydrogen atoms; and

Z^1 and Z^2 are each independently selected from a hydrogen atom, and a hydroxyl group.

[Claim 6]

A compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1 which has Raf inhibiting effect and angiogenesis inhibiting effect and is

used for treating cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes.

[Claim 7]

A pharmaceutical composition comprising a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of any one of claims 1 to 5 as an active ingredient.

[Claim 8]

An Raf inhibitor or an angiogenesis inhibitor comprising a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of any one of claims 1 to 5 as an active ingredient.

[Claim 9]

A preventive or therapeutic agent for a disease selected from cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes which comprises a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of any one of claims 1 to 5 as an active ingredient.

[Name of Document] Specification

[Title of Invention] HETEROARYL PHENYLUREA DERIVATIVES

[Technical Field to which the Invention Pertains]

[0001]

The present invention relates to a novel heteroaryl phenylurea derivative, a pharmaceutically acceptable salt thereof, a synthetic intermediate of the derivative and a pharmaceutical composition comprising the derivative or its pharmaceutically acceptable salt.

[0002]

Particularly, the present invention relates to a compound useful as a Raf inhibitor and an angiogenesis inhibitor. The above-described compound is useful for treating growth diseases, for example, cancer, psoriasis or atherosclerosis and is also useful for treating chronic rheumatoid arthritis and diabetes.

[Background Art]

[0003]

The Ras signal transduction pathway responds to various extracellular signals, for example, growth factors, cytokines and an extracellular matrix (ECM) through the cell-surface receptors to play an important role in proliferation, differentiation and transformation of cells.

[0004]

The activation of the Ras protein in normal cells begins by the interaction of such extracellular signals as growth facters with the cell-surface receptors, and then the activated Ras protein interacts with Raf, a serine-

threonine protein kinase, to activate Raf (see Non-patent Document 1 and Non-patent Document 2). It is known that with Raf, there are three types of isoforms of A-Raf of 68 Kd, B-Raf of 95 and Raf-1 (c-Raf) of 74 Kd, and each is different in the aspects of the interaction with the Ras protein, the capacity of activating the substrate MEK, the expression and distribution in organs and the like, and the study with the use of a knockout mouse shows that all three A-Raf, B-Raf and Raf-1 are essential in survival. The activated Raf successively activates the substrate MEK by phosphorylation and the activated MEK activates ERK 1 and ERK 2 (MAPK). The activated ERK finally activates various substrates such as transcription factors in the cell nucleus and cytoplasma to bring about cellular changes (proliferation, differentiation and transformation) in response to the extracellular signals. These cellular changes including proliferation in normal cells are appropriately regulated but it is observed that in human cancer cells, about 20% of the Ras protein is always mutated to be in an activated state (GTP complex) and it is known that as a result, the growth signal to the Raf/MEK/ERK cascade is maintained to play an important role in the growth of human cancer cells (see Non-patent Document 3). Further, in the recent study, it is reported that the mutation of B-raf is confirmed in 66% of melanormas, 15% of colon cancers and 14% of liver cancers, and the Raf/MEK/ERK cascade is in an activated state (see Non-patent Document 4).

[0005]

In addition to the role as a direct downstream effector of the Ras protein in the Raf/MEK/ERK cascade as described above, the Raf kinase is known to play a key role in controlling the apoptosis of cells by various mechanisms (see Non-patent Document 5).

[0006]

Thus, the techniques of blocking the Ras signal transduction pathway which plays an important role in the proliferation of cancer cells by inhibiting the Raf kinase as a target can be thought useful. Actually, it is reported that by inhibiting the expression of Raf with the RNA antisense, the growth of various human cancers is inhibited in vitro and in vivo (see Non-patent Document 6).

[0007]

Tumor cells take in oxygen and nutrients necessary for survival and growth from the surrounding environment. In a solid tumor, these substances are supplied by simple diffusion until the solid cancer reaches a certain size. However, as the solid tumor grows to form a region 1 to 2 mm or more apart from the nearest blood vessel, this region forms a hypoxia region where the oxygen concentration is low, the nutrients are poor and the pH is low. Against to these stresses, tumor cells respond by various angiogenesis factors to stimulate the formation of a new blood vessel from the neighboring vascular endothelial cells. The angiogenesis thus started is thought to be essential in the growth of the solid tumors. There are a number of reports

which suggests the relationship between VEGF (vascular endothelial growth factor), a growth factor specific for the vascular endothelial cells and cancers, and the drugs which target VEGF or the tyrosine kinase activity of its receptors have recently been developed (see Non-patent Document 7 and Non-patent Document 8). Up to now, it is known that VEGF bonds to three types of receptor tyrosine kinases of VEGFR-1 (flt-1), VEGFR-2 (KDR) and VEGF-3 (Flt-4), and since KDR performs strongly ligand-dependent autophosphorylation, KDR is thought to be essential to VEGF-dependent biological responses including angiogenesis.

[0008]

On the other hand, a number of factors which anticipate in angiogenesis are known in addition to VEGF, and the development of inhibitors of such growth fators which play a key role in angiogenesis and specifically act on vascular endothelial cells to inhibit their growth and functions is strongly desired as therapeutic agents for angiogenic diseases such as cancers.

[0009]

With respect to the relationship between the two cancer treatment targets, that is, Raf and angiogenesis, an interesting report has recently been made. The activation of B-Raf and Raf-1 depends on not only the Ras protein but also growth factor signals. Basic fibroblast growth factor (b-FGF) activates Raf-1 through PAK-1 (p21-activated protein kinase-1) by the phosphorylation of serine 338 and 339 non-dependently to MEK 1 to protect endothelial cells

from apoptosis. The VEGF signal activates Raf-1 through Src kinase by phosphorylation of tyrosine 340 and 341 dependently to MEK 1 to protect endothelial cells. By this report, it has been clarified that Raf plays a key role in not only the growth of cancer cells but also the control of survival of endothelial cell on angiogenesis (see Non-patent Document 9).

[0010]

Further, angiogenesis is a physiological phenomenon essential in embryonic formation of the fetal period, wound healing of an adult, the menstrual period of an adult female and the like but it is reported that abnormality of angiogenesis in an adult individual relates to psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetic diseases (see Non-patent Document 10 and Non-patent Document 11), and inhibition of angiogenesis is useful for treating these diseases with the abnormality of angiogenesis.

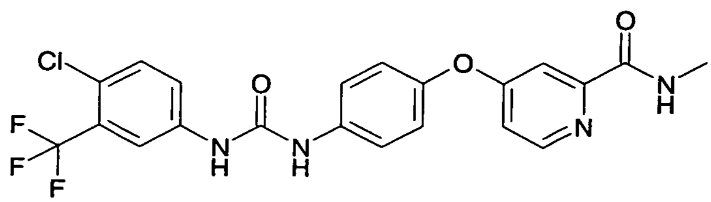
[0011]

Heretofore, a number of urea compounds which exhibit anticancer action by inhibiting any of Raf and kinases relating to angiogenesis (see Patent Documents 1 to 12). However, these compounds have a problem of solubility in water due to the high hydrophobicity and high crystallinity attributed to the phenylurea skeleton. Particularly in the case of oral drugs, the property of inferior solubility in water tents to lead to severe problems in clinical development such as poor bioavailability, unstable effecacy

due to the individual difference in PK among patients or tendency of accumulation (see Non-patent Document 11 and Non-patent 13). For example, it is reported that the following compound Bay 43-9006 (Patent Document, Example 41):

[0012]

[Formula 1]



[0013]

is a Raf-1 and B-RAF inhibitor and is also an inhibitor of kinases relating to the angiogenesis and the progression of a cancer including KDR, VEGFR-3, Flt-3, c-KIT and PDGFR-β (see Non-patent Document 15). However, the results of the phase I clinical study of the compound are reported (see Non-patent Document 15) and the compound is pointed out to have problems of high interpatient PK variability, tendency of accumulation upon multiple dosing and the like due to high lipophilicity and low water solubility.

[Patent Document 1] International Publication No.98/52559 Pamphlet

[Patent Document 2] International Publication No.99/32106 Pamphlet

[Patent Document 3] International Publication No.99/32436 Pamphlet

[Patent Document 4] International Publication No.99/32455 Pamphlet

[Patent Document 5] International Publication No.00/42012 Pamphlet

[Patent Document 6] International Publication No.02/62763 Pamphlet

[Patent Document 7] International Publication No.02/85857 Pamphlet

[Patent Document 8] International Publication No.03/47579 Pamphlet

[Patent Document 9] International Publication No.03/68223 Pamphlet

[Patent Document 10] International Publication No.03/40228 Pamphlet

[Patent Document 11] International Publication No.03/40229 Pamphlet

[Patent Document 12] International Publication No.03/68746 Pamphlet

[Non-patent Document 1] Trends Biochem. Sci., Vol.19, 474-480, 1994

[Non-patent Document 2] Science, Vol.264, 1463-1467, 1994

[Non-patent Document 3] Annual Reports in Medicinal Chemistry, Vol.29, 165-174, 1994

[Non-patent Document 4] Nature, Vol.417, 949, 2002

[Non-patent Document 5] Biochemical Pharmacology, Vol.66, 1341-1345, 2003

[Non-patent Document 6] Nature, Vol.349, 426-429, 1991

[Non-patent Document 7] J. Clinical Oncology, Vol.21, 60-65,

2003

[Non-patent Document 8] Expert Opinion Investigational Drugs, Vol.12, 51-64, 2003,

[Non-patent Document 9] Science, Vol.301, 94-96, 2003

[Non-patent Document 10] New England Journal of Medicine, Vol.333(26), 1757-63, 1995

[Non-patent Document 11] Angiogenesis, Vol.5(4), 237-256, 2002

[Non-patent Document 12] Pharmazeutische Industrie, Vol.64(8), 800-807, 2002

[Non-patent Document 13] Pharmazeutische Industrie Vol.64(9), 985-991, 2002

[Non-patent Document 14] AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Proceedings, p.69, No.A78, 2003

[Non-patent Document 15] American Society of Clinical Oncology, Annual Meeting (May 18 to May 21, 2002) Abstracts, Nos. 121, 1816 and 1916, 2002.

[Disclosure of the Invention]

[Problems to be Solved by the Invention]

[0014]

The present invention has an object to provide a compound which has high Raf inhibition activity and angiogenesis inhibition activity and is useful as an effective therapeutic and preventive agent for a disease with pathologic angiogenesis, for example, cancer and

metastasis of cancer, its preparation method, an intermediate useful for its preparation and furthermore pharmaceutical composition containing these compounds.
Means to Solve the Problem.
[Measures of Solving the Problems]

[0015]

As the results of strenuously developing heteroaryl phenylurea derivatives having excellent Raf and angio-genesis inhibition effects by the present inventors, it has been found that derivatives having a specified structure not only exhibit excellent both inhibition actions but also excel in solubility to water and shows high and stable oral bioavailability and are useful as preventive or therapeutic agents excellent in safety for proliferative diseases, and the present invention has been completed.

[0016]

Compared to BAY 43-9006 disclosed in Patent Document 5 (international Publication No. 00/42012 Pamphlet), the compounds of the present invention have excellent solubility in water. Therefore, the compounds of the present invention are expected to have less interpatient variability in PK parameters such as Cmax, AUC value and half-life, and excellent and stable oral absorption, when administered orally. Further, the compounds of the present invention cause less body weight reduction in a dosage to exhibit the same therapeutic effect as BAY 43-9006 in an animal model and accordingly are useful as safer therapeutic or preventive agents (therapeutic agents,

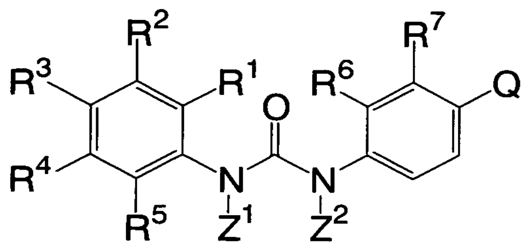
especially).

[0017]

Namely, according to one aspect of the present invention, there is provided a compound represented by formula (1):

[0018]

[Formula 2]



(1)

[0019]

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group which may be substituted with one or more halogen atoms and a C_1-C_6 alkoxy group which may be substituted with one or more halogen atoms;

R^6 and R^7 are each independently selected from a hydrogen atom and a halogen atom;

Z^1 and Z^2 are each independently selected from a hydrogen atom, a hydroxyl group and -$O(CHR^{11})OC(=O)R^{12}$;

wherein

R^{11} is a hydrogen atom or a C_1-C_6 alkyl group; and

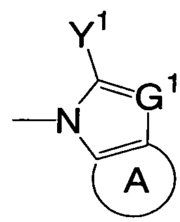
R^{12} is a pyrrolidinyl group, a piperidinyl group, a morpholinyl group, a piperazinyl group, an amino C_1-C_6 alkyl group, a mono- or di(C_1-C_6 alkyl)amino C_1-C_6

alkyl group, an amino C_1-C_6 alkylamino group or a mono- or di(C_1-C_6 alkyl)-amino C_1-C_6 alkylamino group;

Q is a group of the formula:

[0020]

[Formula 3]



[0021]

wherein

G^1 is C-Y^2 or N;

ring A is a benzene ring or a 5- to 6-membered unsaturated heterocycle; a nitrogen atom present in the heterocycle may be an N-oxide; and the ring A may be substituted with one to three same or different substituents W;

Y^1 and Y^2 are each independently selected from a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxy C_1-C_6 alkyl group, a C_1-C_6 alkoxy C_1-C_6 alkoxy group, an amino C_1-C_6 alkoxy group, a (C_1-C_6 alkyl)amino C_1-C_6 alkyl group, an amino group, a (C_1-C_6 alkyl)amino group and a di(C_1-C_6 alkyl)amino group;

W is a halogen atom, a nitro group, a cyano group, a hydroxyl group, -NRaRb, -N=C(-Rc)NRaRb, -CONRaRb, -OC(=O)NRaRb, -SO_2NRaRb, -N(-Ra)C(=O)NRa'Rb', -N(-Ra)C(=O)ORd, -N[C(=O)ORd][C(=O)ORd'],

$-C(=O)ORd$, $-S(=O)_m-Rd$, $-O-Rd$, $-OC(=O)Rc$, $-N(-Ra)C(=O)Rc$, $-N[C(=O)Rc][C(=O)Rc']$, $-N(-Ra)SO_2Rc$, $-N(SO_2Rc)(SO_2Rc')$, $-C(=NORd)NRa'Rb'$, $-C(=NRa)NRa'Rb'$, $-C(=NORa)Rc$, $-C(=O)Rc$, a C_1-C_6 alkyl group which may be substituted with one or more Y^3, a C_2-C_7 alkenyl group which may be substituted with one or more Y^3, a C_2-C_7 alkynyl group which may be substituted with one or more Y^3, an aryl group which may be substituted with one or more Y^3 or a heteroaryl group which may be substituted with one or more Y^3;

Ra, Ra', Rb, Rb', Rc, Rc', Rd and Rd' are each independently selected from a hydrogen atom, a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, $-[(C_1$-C_6 alkylene$)-O]_n-(C_1$-C_3 alkyl$)$, an aryl group or a heteroaryl group, a pyrrolidinyl group and a pyperidinyl group (wherein the pyrrolidinyl group or the pyperidinyl group may be substituted with a C_1-C_3 alkyl group); or

Ra and Rb, Ra' and Rb', Ra and Rd, Ra and Ra', Ra and Rc, Rc and Rc' or Rd and Ra' may form a saturated or unsaturated 5- to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

Ra, Rb, Ra', Rb', Rc, Rc', Rd and Rd' each may be substituted with one to three same or different substituents selected from Y^3;

m is an integer selected from 0 to 2;

n is an integer selected from 1 to 4;

Y^3 is a halogen atom, -NRxRy, -C(=O)ORz, -ORz, -CONRxRy, -OC(=O)NRxRY, $-SO_2NRxRy$, -N(-Rx)C(=O)NRx'Ry', -N(-Rx)C(=O)ORz, -S-Rz, -SO-Rz, $-SO_2-Rz$, -OC(=O)Rz, -N(Rx)C(=O)Rz, -C(=NORz)NRx'Ry', -C(=NRx)NRx'Ry', -C(=NORx)Rz, $-[O-(C_1-C_6\ \text{alkylene})]_n-O(C_1-C_3\ \text{alkyl})$, $-N(-Rx)-(C_1-C_6\ \text{alkylene})-O(C_1-C_3\ \text{alkyl})$, -CORz, a C_1-C_6 alkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, an aryl group or a heteroaryl group;

Rx, Rx', Ry, Ry' and Rz are each independently selected from a hydrogen atom and a C_1-C_4 alkyl group;

Rx and Ry, Rx and Rx', Rx and Rz or Rz and Rx' may form a saturated or unsaturated 5-to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

a pharmaceutically acceptable salt thereof or a prodrug thereof.

[0022]

In the above-described formula (1), Y^2 is preferably a hydrogen atom. Further, R^{11} is preferably a hydrogen atom or a methyl group, and R^{12} is preferably a pyrrolidinyl group or a piperazinyl group.

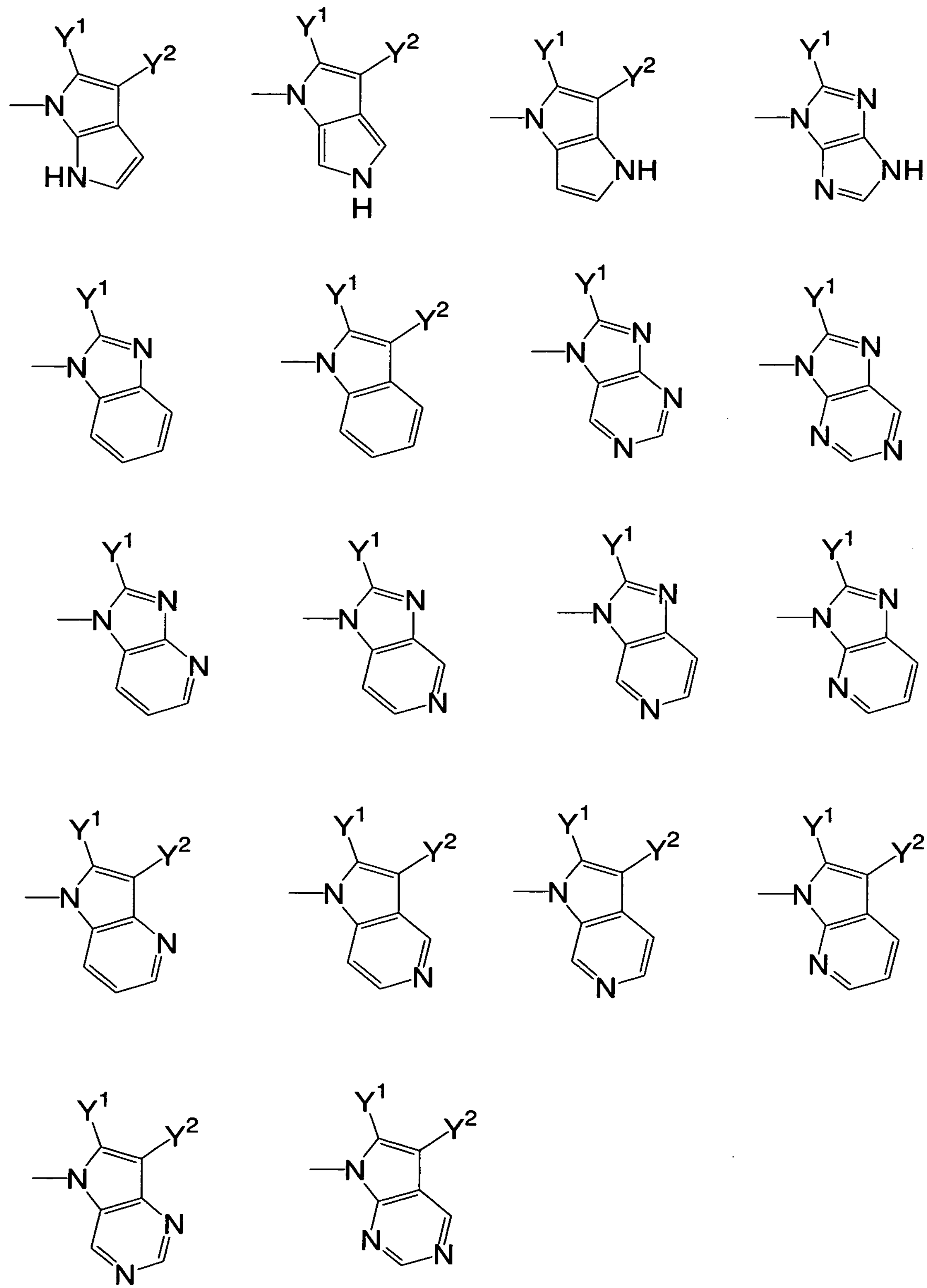
[0023]

According to another aspect of the present invention, there is provided a compound of formula (1), a

pharmaceutically acceptable salt thereof or a prodrug thereof wherein Q is a group of the formula selected from:

[0024]

[Formula 4]



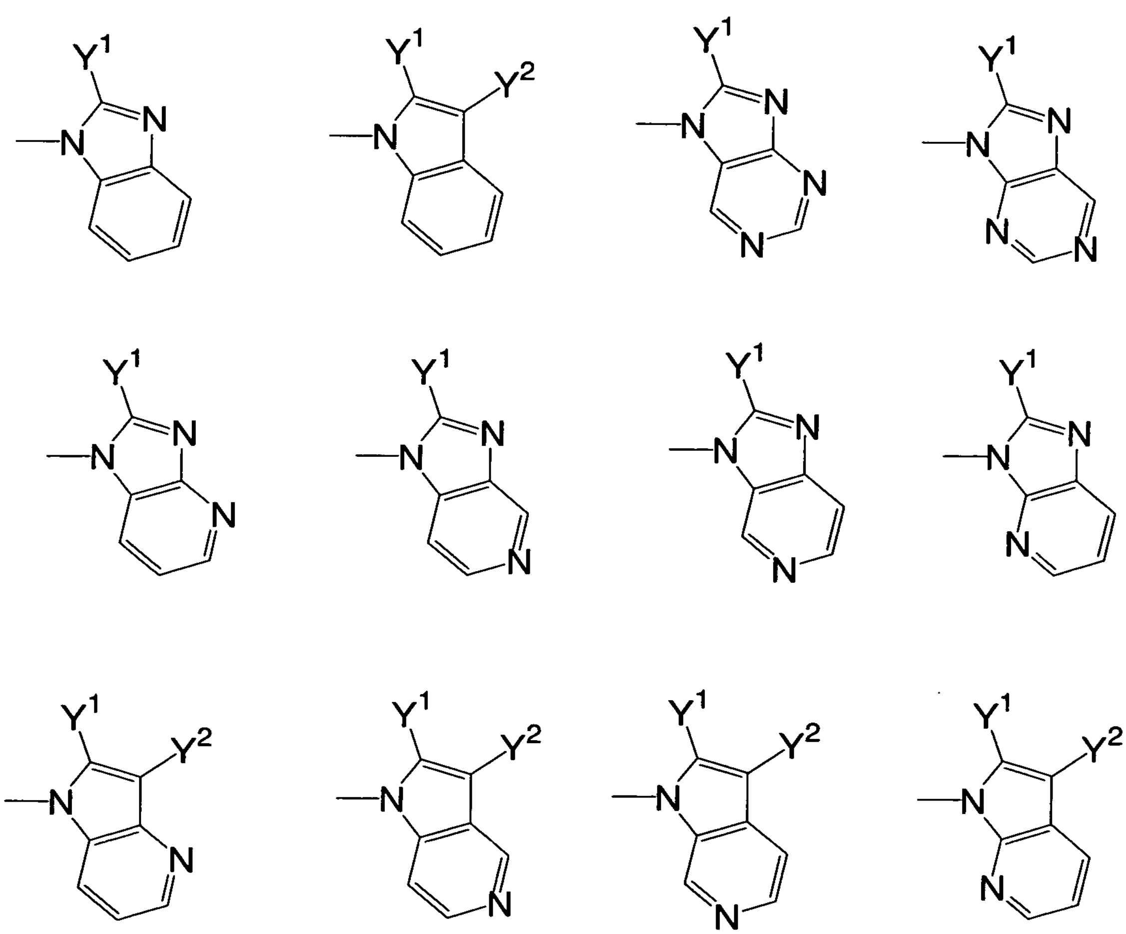
[0025]

which may be substituted with one to three same or different substituents W.

[0026]

Herein, Q may be a group of the formula selected from:

[Formula 5]



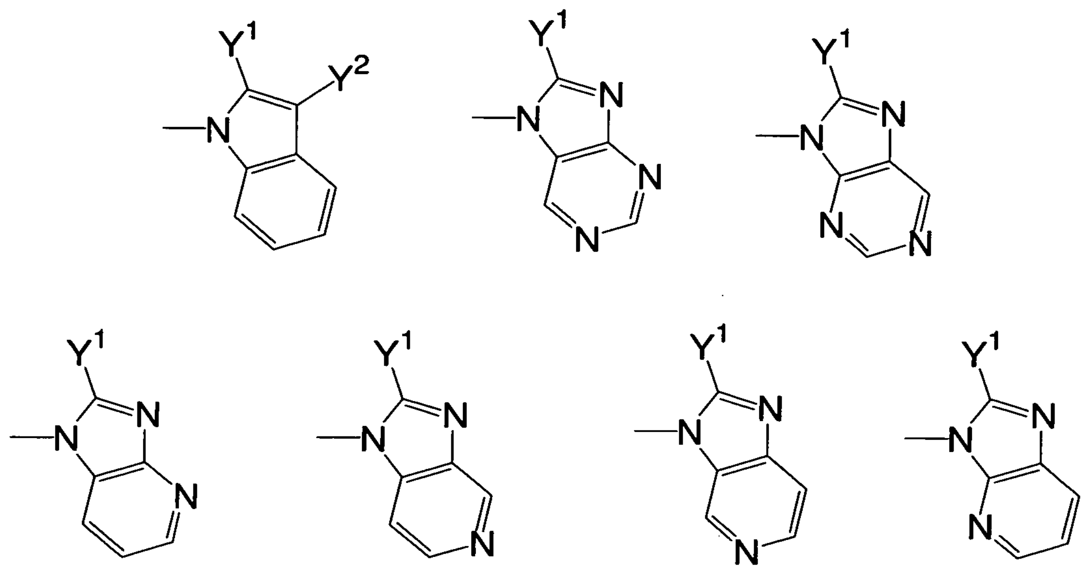
[0027]

which may be substituted with one to three same or different substituents W.

Further, Q may be a group of the formula selected from:

[0028]

[Formula 6]



[0029]

which may be substituted with one to three same or different substituents W.

According to a further aspect of the present invention, there is provided a compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a chlorine atom, a fluorine atom, a bromine atom and a trifluoro-methyl group;

R^6 and R^7 are hydrogen atoms; and

Z^1 and Z^2 are each independently selected from a hydrogen atom and a hydroxyl group.

[0030]

According to another aspect of the present invention, the above-described compound of formula (1), a

pharmaceutically acceptable salt thereof or a prodrug thereof which has Raf inhibition and angiogenesis inhibition actions and is used in treating a cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes is provided.

[0031]

According to a further aspect of the present invention, a pharmaceutical composition comprising the above-described compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof as an active ingredient is provided.

[0032]

According to a still further aspect of the present invention, a Raf inhibitor or an angiogenesis inhibitor comprising the above-described compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof as an active ingredient is provided.

[0033]

According to a further aspect of the present invention, a preventive or therapeutic agent for a disease selected from cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes which contains the above-described compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof as an active ingredient is provided.

[Embodiments of the Invention]

[0034]

The term "halogen", as used in the present invention,

means a fluorine atom, a chlorine atom, a bromine atom and iodine atom.

The term "C_1-C_3 alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 3 carbon atoms and includes, for example, methyl, ethyl, n-propyl and i-propyl.

[0035]

The term "C_1-C_4 alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms and include, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butly, sec-butyl and tert-butyl.

[0036]

The term "C_1-C_6 alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms and includes, for example, "C_1-C_4 alkyl group" such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl and t-butyl, and further includes n-pentyl, 3-methylbutyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3-ethylbutyl and 2-ethylbutyl.

[0037]

The term "C_1-C_{10} alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 10 carbon atoms and includes, for example, "C_1-C_4 alkyl group" and "C_1-C_6 alkyl group", and further includes n-heptyl, n-octyl, n-nonyl and n-decanyl.

[0038]

The term "C_3-C_8 cycloalkyl group", as used in the present invention, means as cyclic or partially cyclic alkyl group having 3 to 8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, hexylcyclomethyl, cyclo-propyl substituted with a C_1-C_5 alkyl, cyclopentyl substituted with a C_1-C_3 alkyl group and cyclohexyl substituted with a C_1-C_2 alkyl group.

[0039]

The term "C_1-C_6 alkoxy group", as used in the present invention, means an alkyloxy group having a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms as an alkyl moiety and includes, for example, methoxy, n-propoxy, i-propoxy, n-butoxy, s-butyoxy, i-butoxy, t-butoxy, n-pentoxy, 3-methylbutoxy, 2-methylbutoxy, 1-methylbutoxy, 1-ethylpropoxy, n-hexyloxy, 4-methylpentoxy, 3-methyl-pentoxy, 2-methylpentoxy, 1-methylpentoxy, 3-ethylbutoxy and 2-ethylbutoxy.

[0040]

The term "C_2-C_8 alkenyl group", as used in the present invention, means a straight-chain or branched-chain alkenyl group having 2 to 8 carbon atoms and include, for example, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), propen-2-yl and 3-butenyl (homoallyl).

[0041]

The term "C_2-C_8 alkynyl group", as used in the present invention, means a straight-chain or branched-chain alkynyl

group having 2 to 8 carbon atoms and include, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl.

[0042]

The term "aryl group", as used in the present invention, means a C_6-C_{10} aromatic hydrocarbon group and include, for example, aphenyl, 1-naphthyl and 2-naphthyl.

The term "heteroaryl group", as used in the present invention, means a 5- to 10-membered aromatic heterocyclyl group containing one or more heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom and include, for example, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolyl. The substituting position of the heteroaryl group may be any substitutable position on a carbon atom or a nitrogen atom and is not particularly limited.

[0043]

The term "unsaturated 5- to 6-membered heterocycle", as used in the present invention, means a heterocycle which contains one or more heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom and has an unsaturated bond and 5 to 6 atoms present in the ring and includes an aromatic heterocycle. Specifically "unsaturated 5- to 6-membered heterocycle" includes, for example, pyrrole, imidazole, pyrazole, pyrazoline, pyridine, pyrazine, pyrimidine, pyridazine, triazine, furan,

thiophene, oxazole and thiazole. The substituting position of the heterocyclyl group may be any substitutable position on a carbon atom or a nitrogen atom and is not particularly limited.

[0044]

The term "saturated or unsaturated 5- to 6-membered heterocycle", as used in the present invention, means a saturated or unsaturated heterocycle which contains one or more heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom and has 5 to 6 atoms present in the ring and includes an aromatic heterocycle. Specifically "saturated or unsaturated 5- to 6-membered heterocycle" includes, for example, pyrrolidine, piperidine, piperazine, pyrrole, imidazole, imidazoline, pyrazole, pyrazoline, oxazoline, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, hexamethylene-imine, furan, tetrahydrofuran, thiophene, tetrahydro-thiophene, dioxolane, oxathiolane and dioxane. The substituting position of the heterocyclyl group may be any substitutable position on a carbon atom or a nitrogen atom and is not particularly limited.

[0045]

In the present invention, the "aryl group" and the "heteroaryl group" may optionally be substituted with at least one halogen atom, C_1-C_6 alkyl or C_1-C_6 alkoxy. The number of the substituent may be one to a possibly maximum number from a chemical structural standpoint. The number of the substituent is, for example, 1 to 5, preferably 1 to 3.

[0046]

In the present invention, when the nitrogen atom present in the ring is an N-oxide, the N-oxide includes, for example, a pyridine-N-oxide, a pyrimidine N-oxide, pyridazine N-oxide and a triazine N-oxide.

[0047]

The term "C_1-C_6 alkylene group", as used in the present invention, means a straight-chain or branched-chain divalent alkylene group having 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene (including, for example, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and $-CH(CH_2CH_3)-$, butylenes (including, for example, $-CH_2CH_2CH_2CH_2-$, $-CH(-CH_3)CH_2CH_2-$,$-CH_2CH(-CH_3)CH_2-$, $-CH_2CH_2CH(-CH_3)-$, $-CH(-CH_2CH_3)CH_2-$, $-CH_2CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$ and $-CH(-CH_3)CH(-CH_3)-$.

[0048]

The term "hydroxyl C_1-C_6 alkyl group", as used in the present invention, means an alkyl group substituted with a hydroxyl group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2-hydroxyprorpyl, 1-hydroxypropyl, 2-hydroxy-prop-2-yl and 1-hydroxy-prop-2-yl.

[0049]

The term "C_1-C_6 alkoxy C_1-C_6 alkyl group", as used in the present invention, means an alkyl group substituted with an alkoxy group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and the already defined C_1-C_6

alkoxy group as an alkoxy moiety and include, for example, methoxymethyl, 2-methoxyethyl, 1-methoxyethyl, 3-methoxypropyl, 2-methoxyporpyl, 1-methoxypropyl, 2-methoxy-prop-2-yl, 1-methoxy-prop-2-yl, ethoxymethyl, 2-ethoxyethyl, 1-ethoxyethyl, 3-ethoxypropyl, 2-ethoxypropyl, 1-ethoxypropyl, 2-ethoxy-prop-2-yl and 1-ethoxy-prop-2-yl.

[0050]

The term "amino C_1-C_6 alkyl group", as used in the present invention, means an alky group substituted with an alkyl group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, aminomethtyl, 2-aminoethyl, 1-aminoethyl, 3-aminoprpyl, 1-aminoprpyl, 2-amino-pro-2-yl and 1-amino-pro-2-yl.

[0051]

The term "(C_1-C_6 alkyl)amino group", as used in the present invention, means an amino group substituted with an amino group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, methylamino, ethylamino, n-propylamino and isopropylamino.

[0052]

The term "di(C_1-C_6 alkyl)amino group", as used in the present invention means an amino group substituted with an alkyl group which has the already independently defined two C_1-C_6 alkyl groups as alkyl moieties and includes, for example, dimethylamino, ethylmethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl-n-propylamino and methyl-isopropylamino.

The term "(C_1-C_6 alkyl)amino C_1-C_6 alkyl", as used in

the present invention, means an alkyl group substituted with an alkylamino group which has the already independently defined two C_1-C_6 alkyl groups as alkyl moieties and include, for example, (methylamino)methyl, 2-(methylamino)ethyl, 1-(methylamino)ethyl, 3-(methylamino)-propyl, 2-(methylamino)propyl, 1-(methylamino)propyl, 2-(methylamino)prop-2-yl and 1-(methylamino)-prop-2-yl.

[0053]

The term "di(C_1-C_6 alkyl)amino C_1-C_6 alkyl", as used in the present invention, means an alkyl group substituted with an alkylamino group which has the already independently defined three C_1-C_6 alkyl groups as alkyl moieties and include, for example, (dimethylamino)methyl, 2-(dimethylamino)ethyl, 1-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 2-(dimethylamino)propyl, 1-(dimethylamino)propyl, 2-(dimethylamino)prop-2-yl and 1-(dimethylamino)-prop-2-yl.

[0054]

The term "amino C_1-C_6 alkylamino group", as used in the present invention, means an alkylamino group substituted with an amino group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, (2-aminoethyl)amino, (3-aminopropyl)amino and (4-aminobutyl)amino.

[0055]

The term "mono(C_1-C_6 alkyl)amino C_1-C_6 alkylamino group", as used in the present invention, means an alkylamino group substituted with an alkylamino group which

has the already defined two C_1-C_6 alkyl group as alkyl moieties and includes, for example, (2-(methylamino)ethyl)amino, (2-(ethylamino)ethyl)amino and (3-(methylamino)propyl)amino and (3-(ethylamino)propyl)amino.

[0056]

The term "di(C_1-C_6 alkyl)amino C_1-C_6 alkylamino group", as used in the present invention, means an alkylamino group substituted with an alkylamino group which has the already defined three C_1-C_6 alkyl group as alkyl moieties and includes, for example, (2-(dimethylamino)ethyl)amino, (2-(diethylamino)ethyl)amino, (3-(dimethylamino)propyl)amino and (3-(diethylamino)propyl)amino.

[0057]

In the present invention, when Ra and Rb or Ra' and Rb' are bonded to the same nitrogen atom, Ra and Rb or Ra' and Rb' may form a saturated or unsaturated 5- to 6-membered heterocycle having at least one nitrogen. The heterocycle includes, for example, pyrrole, pyrrolidine, piperazine, pyridine, morpholine and thiomorpholine.

[0058]

In the present invention, the -N(-Ra)C(=O)ORd group may be ring-closed at the bonding position of Ra and Rd to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, oxazolin-2-one and oxazolidin-2-one.

[0059]

In the present invention, the -N(-Ra)C(=O)NRa'Rb'

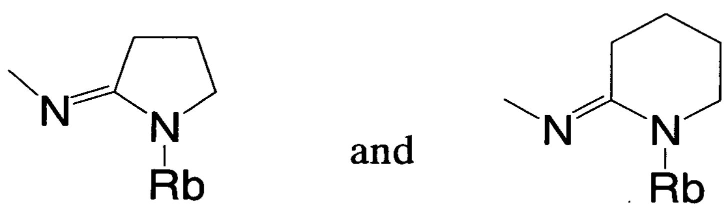
group may be ring-closed at the bonding position of Ra and Ra′ to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, imidazolin-2-one and imidazolidin-2-one.

[0060]

In the present invention, the -N=C(-Rc)NRaRb group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The -N=C(-Rc)NRaRb on forming a heterocycle includes, for example, the formulae:

[0061]

[Formula 7]



[0062]

In the present invention, the -N(-Ra)C(=O)Rc group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, pyrrolin-2-one, pyrrolidin-2-one, piperidin-2-one and morpholin-3-one.

[0063]

In the present invention, the -C(=NORa)Rc group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, isoxazole and

isoxazoline.

[0064]

In the present invention, the $-N(-Ra)SO_2Rc$ group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, isothiazole-1,1-dioxide and isothiazoline-1,1-dioxide.

[0065]

In the present invention, the –N[C(=O)Rc][C(=O)Rc′] group may be ring-closed at the bonding position of Rc and Rc′ to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, pyrrolidin-2,5-dione and piperidine-2,5-dione.

[0066]

In the present invention, the –C(=NORd)NRa′Rb′ group may be ring-closed at the bonding position of Rd and Ra′ to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, oxadiazoline.

[0067]

The present invention includes a salt of the compound represented by formula (1) and a pharmaceutically acceptable salt of a prodrug of the compound. These salts are produced by bringing the compound or the prodrug of the compound into contact with an acid or a base usable in the production of drugs. The salts include, for example, a hydrochloride, a hydrobromide, a hydroiodide, a sulfate, a sulfonate, a phosphate, a phosphonate; a carboxylate such

as an acetate, a citrate, a malate, a salicylate; an alkali metal such as a sodium salt and potassium salt; an alkaline earth metal salt such as a magnesium salt and a calcium salt; and an ammonium salt such as an ammonium salt, an alkylammonium salt, a dialkylammonium salt, a trialkylammonium salt and a tetraalkylammonium salt.

[0068]

The term "prodrug", as used in the present invention, means a derivative of the compound of formula (1) which is converted into the compound of formula (1) or its pharmaceutically accepatable salts by enzymatic or non-enzymatic reaction under physiological conditions. When the prodrug is administered to a patient, it ma be inactive, but in a living body, it is converted to be in the form of the compound of formula (1) which is active.

[0069]

The term "prodrug" in the present invention includes, for example, that:

(1) when the compound of the formula (1) has a hydroxyl group in the molecule, the hydroxyl group is protected with a protective group;

(2) when the compound of the formula (1) has a -NH- group or an amino group in the molecule a compound, the -NH-group or the amino group is protected with a protective group; and

(3) when the compound of the formula (1) has a carboxyl group in the molecule, the carboxyl group is converted to an ester group or an amide group which may be substituted.

[0070]

Herein, examples of the protective group for the hydroxyl group include, for example, a C_1-C_6 alkylcarbonyl group, an arylcarbonyl group, a heteroarylcarbonyl group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylaminocarbonyl group, a di(C_1-C_6 alkyl)amino-carbonyl group, an aryl C_1-C_6 alkyl group, a heteroaryl C_1-C_6 alkyl group, an aryl C_1-C_6 alkylaminocarbonyl group, $-P(=O)(OH)_2$, $-CH_2OP(=O)(OH)_2$, a C_1-C_6 alkyl group, a C_1-C_6 alkylsulfonyl group, an ((amino C_1-C_6 alkyl)carbonyloxy)C_1-C_6 alkyl group and an unsaturated heterocyclic carbonyloxy C_1-C_6 alkyl group. Further, the protected hydroxyl group may be an ester of a natural type or non-natural type amino acid, an ester of a dipeptide, an ester of a tripeptide or an ester of tetrapeptide. Preferred protective groups for the hydroxyl group include, for example, an acetyl group, a glycidyl group, a sarcosyl group, an alanyl, group, a leucyl group and a (5-methyl-2-oxo-1,3-dioxolo-4-yl)methyl group.

[0071]

Examples of the protective group for the -NH- group or amino group include, for example, a C_1-C_6 alkylcarbonyl group, an arylcarbonyl group, a heteroarylcarbonyl group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylaminocarbonyl group, a di(C_1-C_6 alkyl)aminocarbonyl group, an aryl C_1-C_6 alkyl group, a heteroaryl C_1-C_6 alkyl group, an (aryl C_1-C_6 alkyl)aminocarbonyl group, $-P(=O)(OH)_2$, $-CH_2OP(=O)(OH)_2$, a C_1-C_6 alkyl group and a C_1-C_6 alkylsulfonyl group. Further, the protected -NH- group or amino group may be an amide of

a natural type or non-natural type amino acid, an amide of a dipeptide, an amide of a tripeptide amide or an amide of a tetrapeptide. Preferred protective groups for the amino group include, for example, an acetyl group, glycidyl group, sarcosyl group, an alanyl group, a leucyl group, and a (5-methyl-2-oxo-1,3-dioxolo-4-yl)methyl group.

[0072]

Further, the amino group may form a saturated or unsaturated heterocyclyl group such as a phthalimide group, a succinimide group, a glutarimide group or a 1-pyrrolyl group by the protection.

[0073]

When the carboxyl group is converted to an ester group or an amide group which may be substituted, examples of the ester group include, for example, a C_1-C_6 alkyl ester, an aryl ester, a heteroaryl ester, an aryl C_1-C_6 alkyl ester, a heteroaryl C_1-C_6 alkyl ester, a C_1-C_6 alkoxy C_1-C_6 alkyl easter, an aryloxy C_1-C_6 alkyl ester, an aryl C_1-C_6 alkyloxy C_1-C_6 alkyl ester, a hydroxyl C_1-C_6 alkyl ester, an amino C_1-C_6 alkyl ester, a C_1-C_6 alkylamino C_1-C_6 alkyl ester and a di(C_1-C_6 alkyl)amino C_1-C_6 alkyl ester. Preferred ester groups are a methyl ester group, an ethyl ester group, 2-hydroxyethyl ester and a 2-(dimethylamino)-ethyl ester group.

[0074]

The amide group is, for example, an amide group represented by $-C(=O)NR^{21}R^{22}$, and R^{21} and R^{22} can be independently selected from a hydrogen atom, a C_1-C_6 alkyl

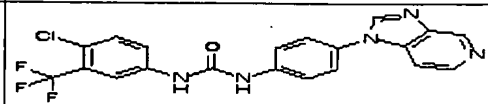
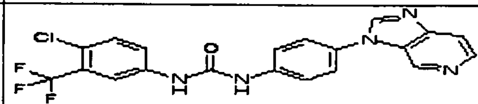
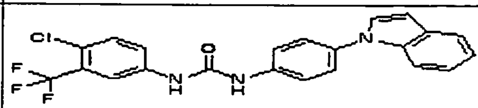
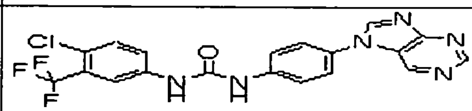
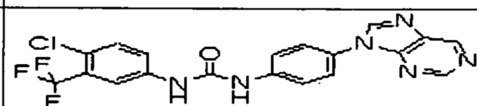
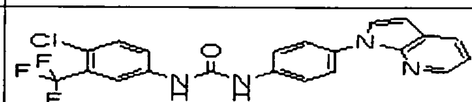
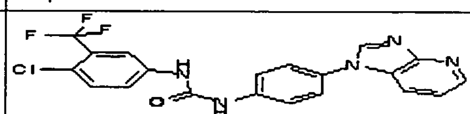
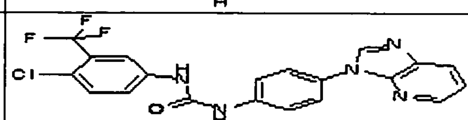
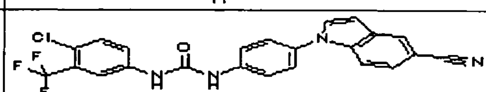
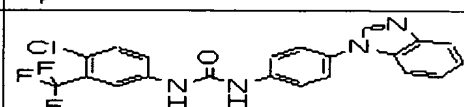
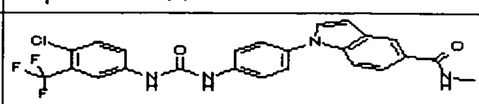
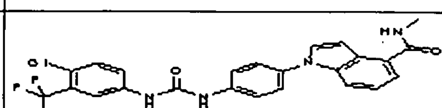
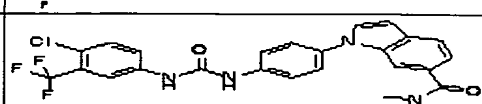
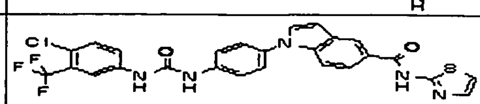
group, an aryl group, a heteroaryl group, an aryl C_1-C_6 alkyl group, a heteroaryl C_1-C_6 alkyl group, a C_1-C_6 alkoxy C_1-C_6 alkyl group, an aryloxy C_1-C_6 alkyl group, an aryl C_1-C_6 alkyloxy C_1-C_6 alkyl group, a hydroxyl C_1-C_6 alkyl group, an amino C_1-C_6 alkyl group, a C_1-C_6 alkylamino C_1-C_6 alkyl group, a di(C_1-C_6 alkyl)amino C_1-C_6 alkyl group, a hydroxyl group and an alkoxy group. R^{21} and R^{22} are preferably each a methyl group, an ethyl group, a 2-hydroxyethyl group or a 2-(dimethylamino)ethyl group.

[0075]

As more specific examples of the compound represented by formula (1) of the present invention, the compounds as described below can be exemplified but the present invention is not limited to them.

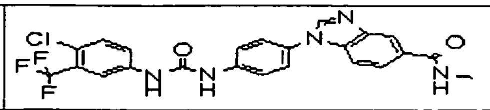
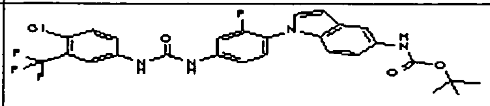
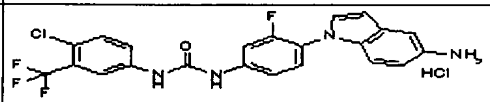
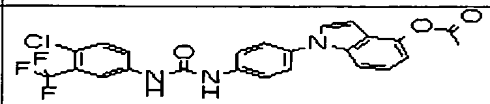
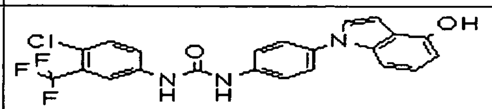
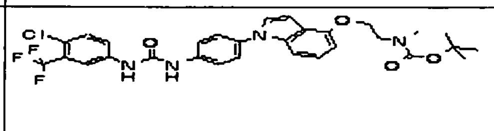
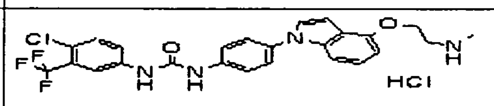
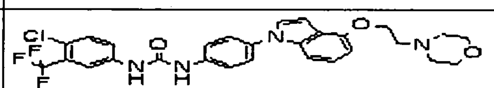
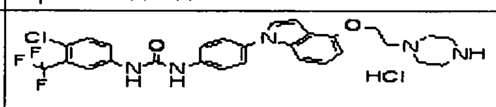
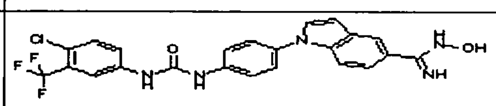
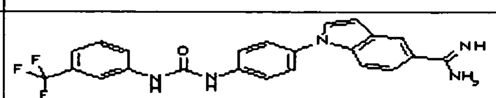
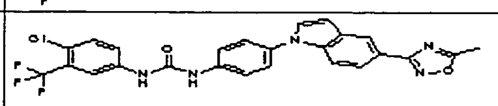
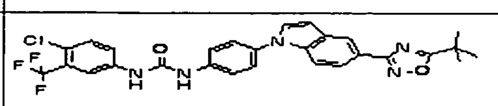
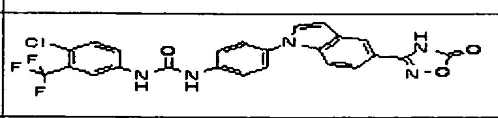
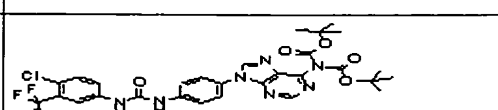
[0076]

[Table 1-1]

	Structural formula	Name of compound	Example No.
1		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-imidazo-[4,5-c]pyridin-1-ylphenyl)urea	Example 1
2		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-imidazo-[4,5-c]pyridin-3-ylphenyl)urea	Example 2
3		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-indol-1-ylphenyl)urea	Example 3
4		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-purin-7-ylphenyl urea	Example 4
5		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-purin-9-ylphenyl)urea	Example 5
6		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-pyrrolo-[2,3-b]pyridin-1-ylphenyl)urea	Example 6
7		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-imidazo-[4,5-b]pyridin-1-ylphenyl)urea	Example 7
8		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-(4-imidazo-[4,5-b]pyridin-3-ylphenyl)urea	Example 8
9		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-[4-(5-cyano-indol-1-yl)phenyl]urea	Example 9
10		1-(4-Benzimidazol-1-ylphenyl)-3-(4-chloro-3-(trifluoro-methyl)phenyl)urea	Example 10
11		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-indole-5-carboxylic acid methylamide	Example 11
12		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-indole-4-carboxylic acid methylamide	Example 12
13		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-indole-6-carboxylic acid methylamide	Example 13
14		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-indole-5-carboxylic acid thiazol-2-ylamide	Example 14

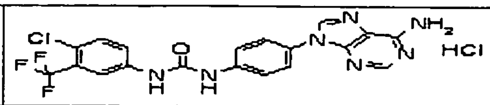
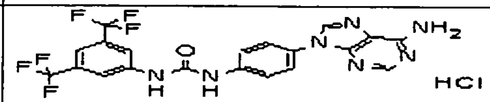
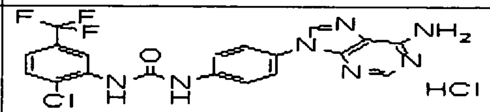
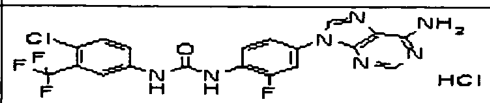
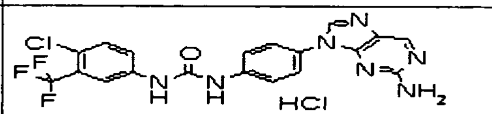
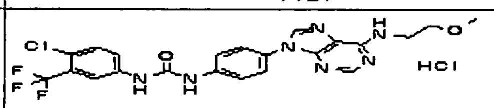
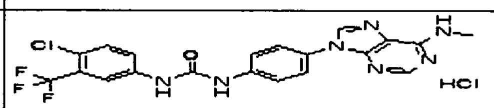
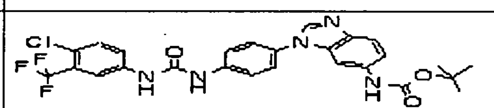
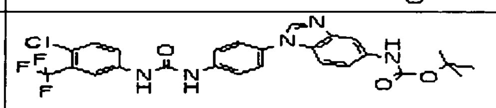
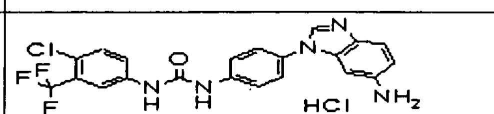
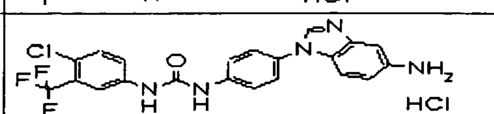
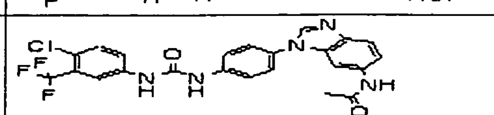
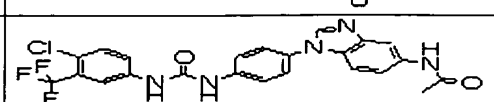
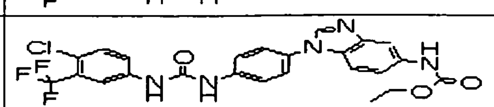
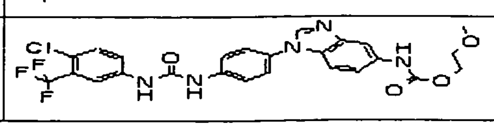
[0077]

[Table 1-2]

15		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-benzimidazole-5-carboxylic acid methylamide	Example 15
16		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]-2-fluoro-phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester	Example 16
17		1-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 17
18		Acetic acid 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indol-4-yl ester	Example 18
19		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-[4-(4-hydroxyindol-1-yl)phenyl]urea	Example 19
20		[2-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester	Example 20
21		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[4-(2-methylamino-ethoxy)indol-1-yl)phenyl]urea hydrochloride	Example 21
22		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[4-(2-morpholin-4-ylethoxy)indol-1-yl]phenyl}urea	Example 22
23		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[4-(2-piperazin-1-ylethoxy)indol-1-yl]phenyl}urea hydrochloride	Example 23
24		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxami-dine	Example 24
25		1-{4-[3-(3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-indole-5-carboxamidine	Example 25
26		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[5-(5-methyl-[1,2,4]oxadiazol-3-yl]indol-1-yl)phenyl}urea	Example 26
27		1-{4-[5-(5-tert-Butyl-[1,2,4]-oxadiazol-3-yl)indol-1-yl] phenyl}-3-(4-chloro-3-(tri-fluoromethyl)phenyl)urea	Example 27
28		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl]-phenyl)urea	Example 28
29		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]-phenyl}urea	Example 29

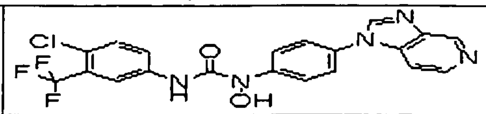
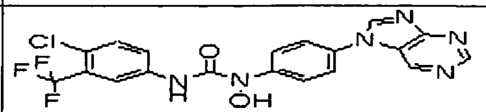
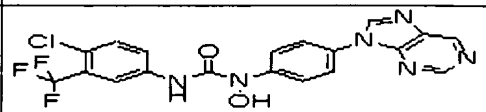
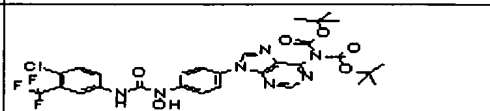
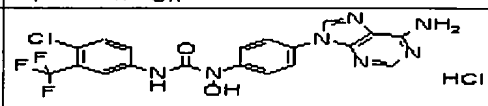
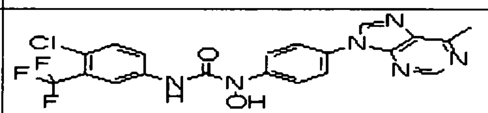
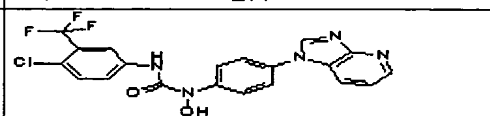
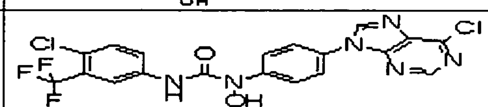
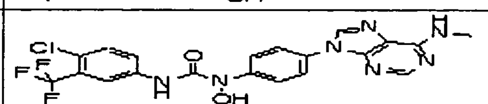
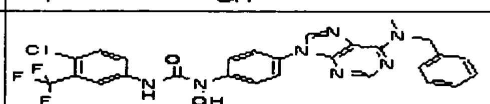
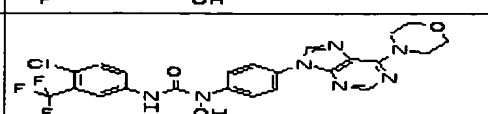
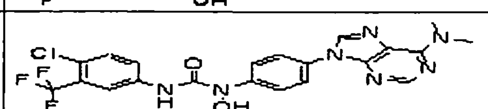
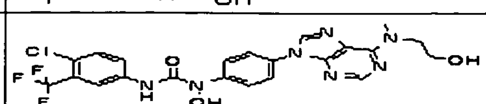
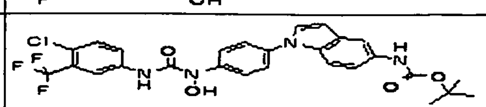
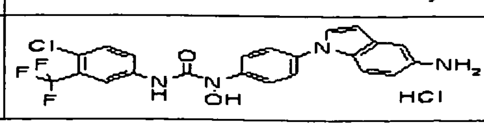
[0078]

[Table 1-3]

30		1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride	Example 30
31		1-[4-(6-Aminopurin-9-yl)phenyl]-3-(3,5-bis-(trifluoromethyl)-phenyl)urea hydrochloride	Example 31
32		1-[4-(6-Aminopurin-9-yl)phenyl]-3-(2-chloro-5-(trifluoromethyl)-phenyl)urea hydrochloride	Example 32
33		1-[4-(6-Aminopurin-9-yl)-2-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 33
34		1-[4-(2-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride	Example 34
35		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(2-methoxy-ethylamino)-purin-9-yl]phenyl}-urea hydrochloride	Example 35
36		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-[4-(6-(methylamino)-purin-9-yl)phenyl]urea hydrochloride	Example 36
37		(3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)carbamic acid tert-butyl ester	Example 37
38		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid tert-butyl ester	Example 38
39		1-[4-(6-Aminobenzimidazol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 39
40		1-[4-(5-Aminobenzimidazol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 40
41		N-(3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)acetamide	Example 41
42		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)acetamide	Example 42
43		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid ethyl ester	Example 43
44		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid 2-methoxyethyl ester	Example 44

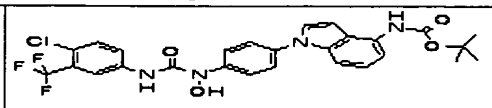
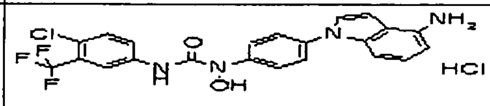
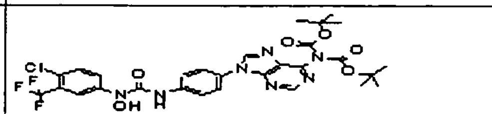
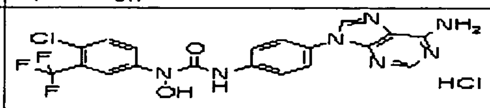
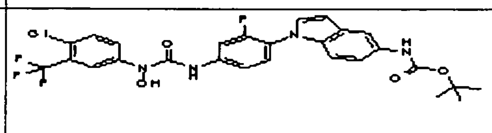
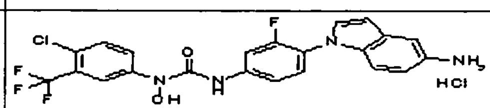
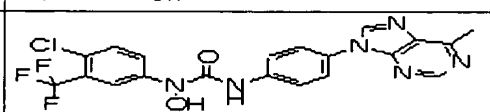
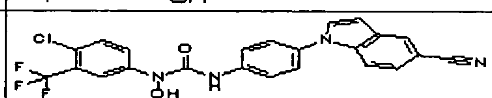
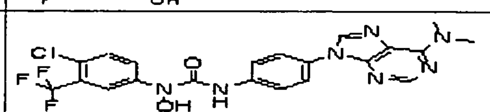
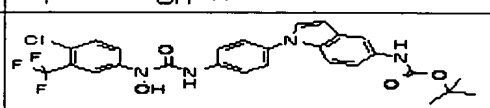
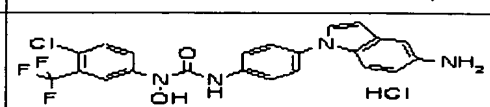
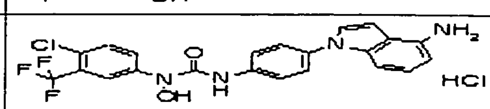
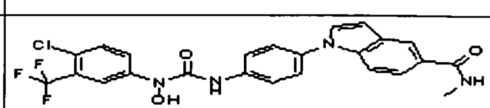
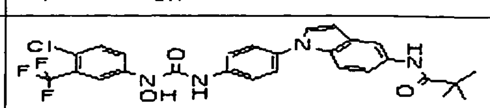
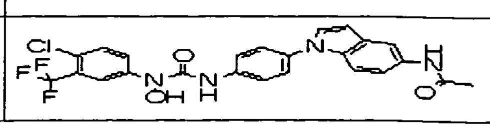
[0079]

[Table 1-4]

45		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hyrdoxy-3-(4-imidazo[4,5-c]pyridin-3-yl-phenyl)urea	Example 45
46		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hyrdoxy-3-(4-purin-7-ylphenyl)urea	Example 46
47		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hyrdoxy-3-(4-purin-9-ylphenyl)urea	Example 47
48		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-3-hydroxyurea	Example 48
49		1-[4-(6-Aminopurin-9-ylphenyl)-3-(4-chloro-3-(trifluoro-methyl)phenyl)-1-hydroxyurea hydrochloride	Example 49
50		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-hydroxy-1-[4-(6-(methylpurin-9-yl)phenyl)-urea	Example 50
51		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-hydroxy-1-(4-imidazo[4,5-b]pyridin-1-yl-phenyl)urea	Example 51
52		1-[4-(6-Chloropurin-9-yl)-phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxy-urea	Example 52
53		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-hydroxy-1-[4-(6-(methylamino)purin-9-yl)-phenyl]urea	Example 53
54		1-{4-[6-(benzyl-methylamino)-purin-9-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea	Example 54
55		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hydroxy-3-[4-(6-morpholin-4-ylpurin-9-yl)-phenyl]urea	Example 55
56		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-[4-(6-dimethylamino-purin-9-yl)-phenyl]-1-hydroxyurea	Example 56
57		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hydroxy-3-(4-{6-[(2-hydroxyethyl)-methyl-amino]purin-9-yl}phenyl)urea	Example 57
58		(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxy-ureido]phenyl}-1H-indol-5-yl)-carbamic acid tert-butyl ester	Example 58
59		1-4-(5-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoro-methyl)phenyl)-1-hydroxyurea hydrochloride	Example 59

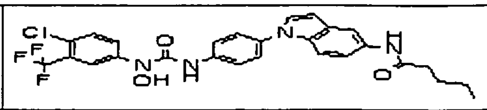
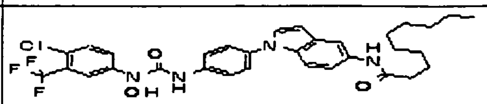
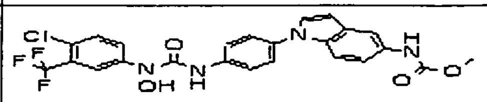
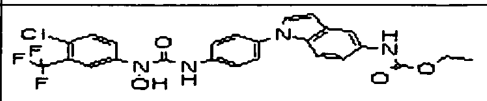
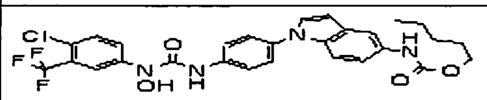
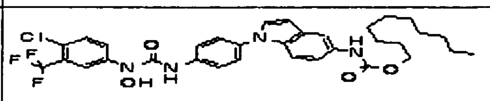
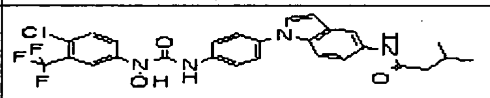
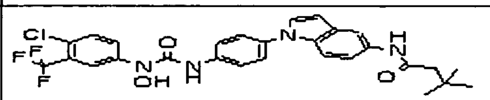
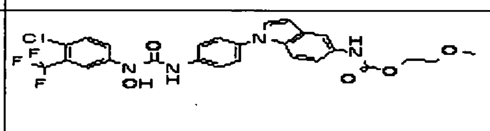
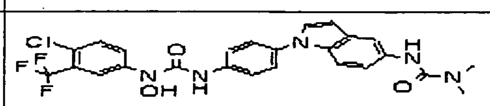
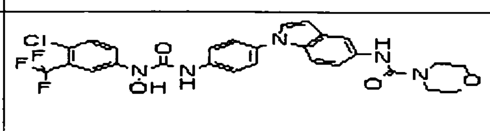
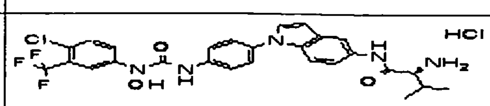
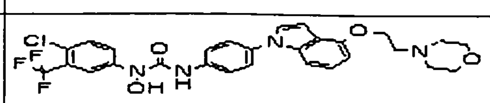
[0080]

[Table 1-5]

60		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]phenyl}-1H-indol-4-yl)-carbamic acid tert-butyl ester	Example 60
61		1-[4-(4-Aminoindol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea hydrochloride	Example 61
62		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)-purin-9-yl]phenyl}-1-hydroxy-urea	Example 62
63		1-[4-(6-Aminopurin-9-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride	Example 63
64		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester	Example 64
65		3-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-1-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea	Example 65
66		3-(4-Choloro-3-(trifluoromethyl)phenyl)-3-hydroxy-1-[4-(6-methylpurin-9-yl)phenyl]urea	Example 66
67		1-(4-Choloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cyanoindol-1-yl)phenyl]-1-hydroxy-urea	Example 67
68		3-(4-Choloro-3-(trifluoromethyl)phenyl)-1-[4-(6-dimethylaminopurin-9-yl)phenyl]-3-hydroxyurea	Example 68
69		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid tert-butyl ester	Example 69
70		1-[4-(5-Aminoindol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride	Example 70
71		1-[4-(4-Aminoindol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride	Example 71
72		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indole-5-carboxylic acid methylamide	Example 72
73		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-2,2-dimethylpropionamide	Example 73
74		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-acetamide	Example 74

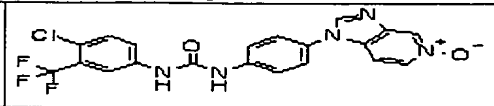
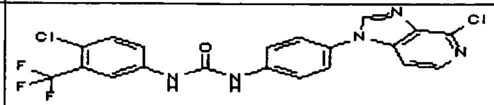
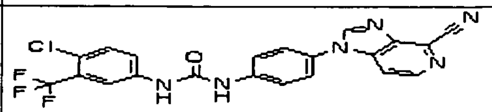
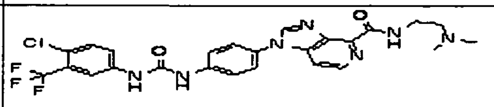
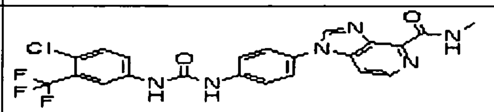
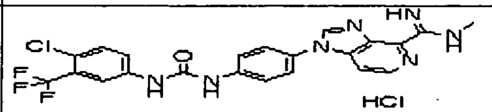
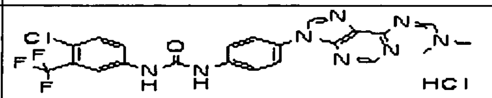
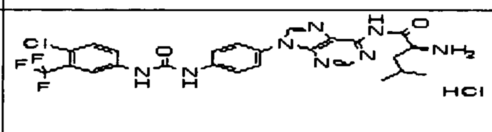
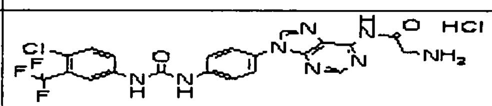
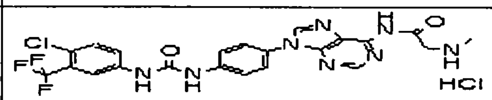
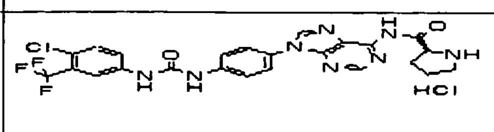
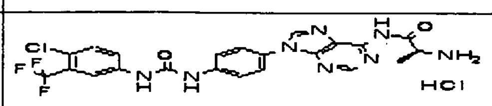
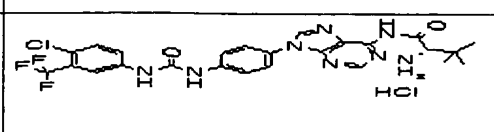
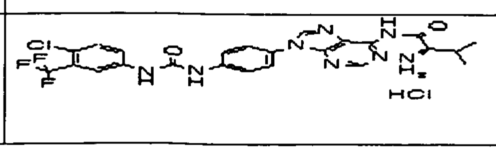
[0081]

[Table 1-6]

75		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-pentanamide	Example 75
76		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-decanamide	Example 76
77		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid methyl ester	Example 77
78		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid ethyl ester	Example 78
79		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid pentyl ester	Example 79
80		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indole-5-yl)-carbamic acid decyl ester	Example 80
81		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3-methylbutylamide	Example 81
82		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3,3-dimethylbutylamide	Example 82
83		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid 2-methoxyethyl ester	Example 83
84		3-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3,3-dimethylurea	Example 84
85		Morpholine-4-carboxylic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-amide	Example 85
86		(2S,3S)-2-Amino-3-methylpentanoic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)-amide	Example 86
87		(S)-2-Amino-N-(1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)-3-methylbutylamide	Example 87
88		1-(4-Choloro-3-(trifluoromethyl)phenyl)-1-hydroxy-3-{4-[4-(2-morpholin-4-yl-ethoxy)-indol-1-yl]phenylurea	Example 88

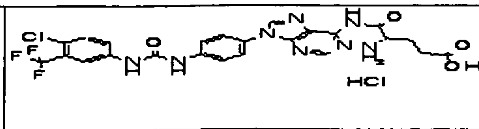
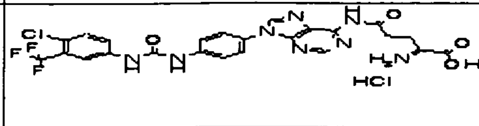
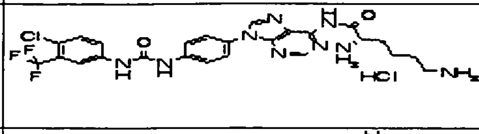
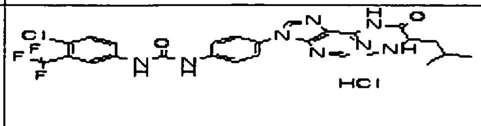
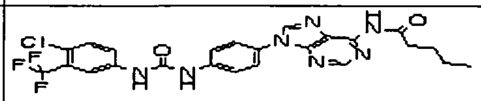
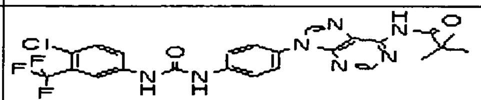
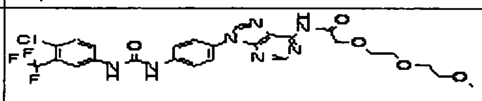
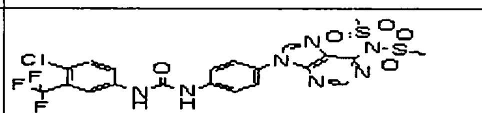
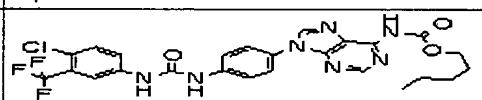
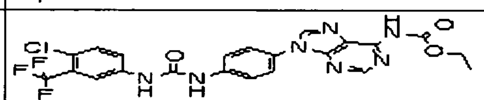
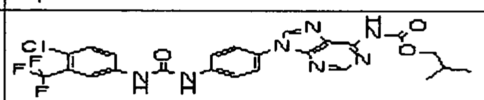
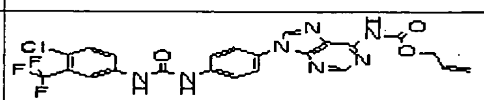
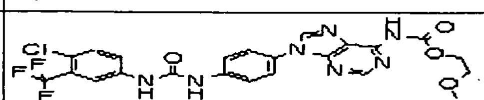
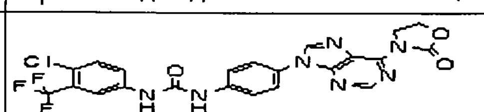
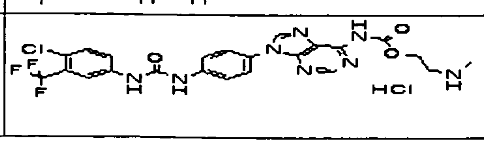
[0082]

[Table 1-7]

89		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea	Example 89
90		1-[4-(4-Chloro-imidazo[4,5-c]-pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea	Example 90
91		1-(4-Chloro-3-(trifluoromethyl) phenyl)-3-[4-(4-cyanoimidazo-[4,5-c]pyridin-1-yl)phenyl]urea	Example 91
92		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-dimethyl-aminoethyl)amide	Example 92
93		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methylamide	Example 93
94		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxamidine hydrochloride	Example 94
95		N'-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-N,N-dimethylformamidine hydro-chloride	Example 95
96		(S)-2-Amino-4-methyl-pentanoic acid 9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride	Example 96
97		2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-acetamide hydrochloride	Example 97
98		N-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-2-methylaminoacetamide hydro-chloride	Example 98
99		(S)-2-Pyrrolidine-2-carboxylic acid 9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride	Example 99
100		(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)propionamide hydrochloride	Example 100
101		(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3,3-dimethylbutylamide hydrochloride	Example 101
102		(R)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3-methylbutylamide hydro-chloride	Example 102

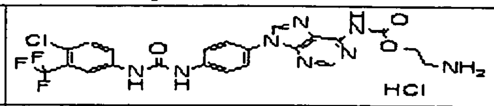
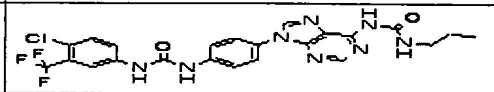
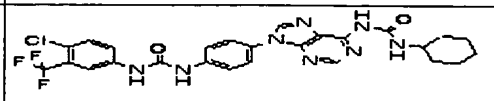
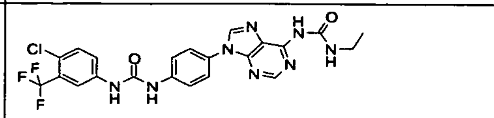
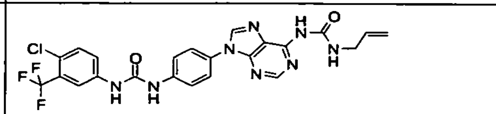
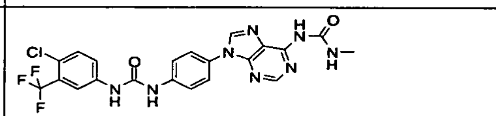
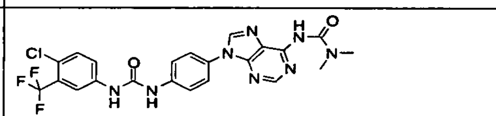
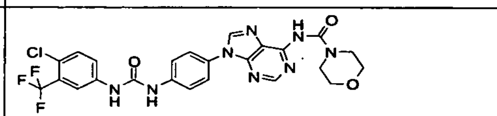
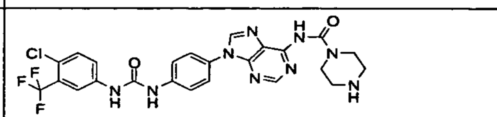
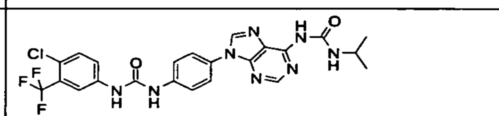
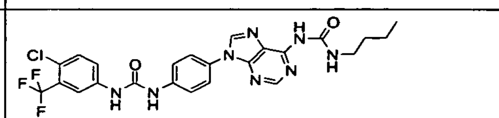
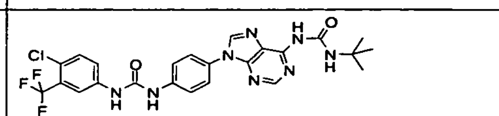
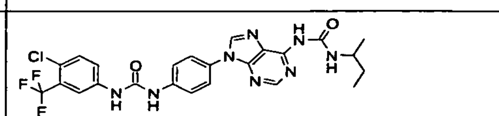
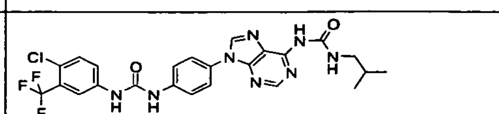
[0083]

[Table 1-8]

103		(S)-4-Amino-4-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride	Example 103
104		(S)-2-Amino-4-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride	Example 104
105		(S)-2,6-Diaminohexanoic acid (9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride	Example 105
106		(S)-4-Methyl-2-methylamino-pentanoic acid (9-{4-[3-(4-chloro-3-(tri-fluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride	Example 106
107		Pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)amide	Example 107
108		N-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-2,2-dimethylpropionamide	Example 108
109		N-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-2-[2-(2-methoxyethoxy)ethoxy]acetamide	Example 109
110		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(di-methanesulfonylamino)purin-9-yl]phenyl}urea	Example 110
111		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid pentyl ester	Example 111
112		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid ethyl ester	Example 112
113		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid isobutyl ester	Example 113
114		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid allyl ester	Example 114
115		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid 2-methoxyethyl ester	Example 115
116		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2-oxo-oxazolidin-3-yl)purin-9-yl]phenyl}urea	Example 116
117		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid 2-methylamino-ethyl ester hydrochloride	Example 117

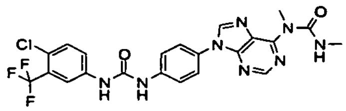
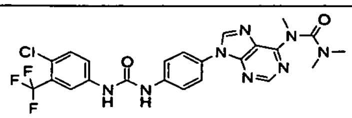
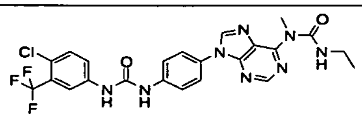
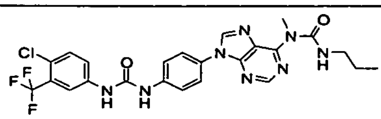
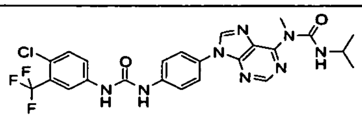
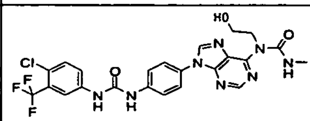
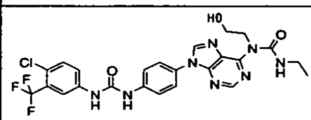
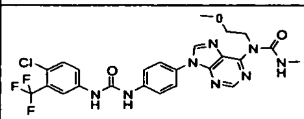
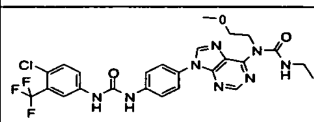
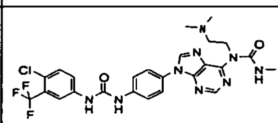
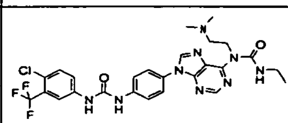
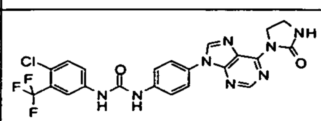
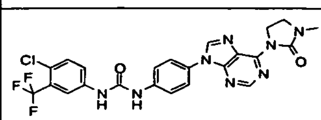
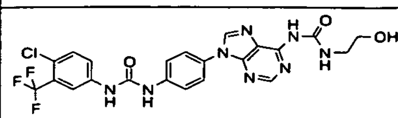
[0084]

[Table 1-9]

118		(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid 2-amino-ethyl ester hydrochloride	Example 118
119		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-propylurea	Example 119
120		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-cyclohexylurea	Example 120
121		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethylurea	Example 121
122		1-Allyl-3-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-urea	Example 122
123		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-methylurea	
124		3-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1,1-dimethylurea	
125		Morpholine-4-carboxylic acid (9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide	
126		Piperidine-1-carboxylic acid (9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide	
127		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-isopropylurea	
128		1-Butyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-urea	
129		1-tert-Butyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea	
130		1-sec-Butyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea	
131		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-isobutylurea	

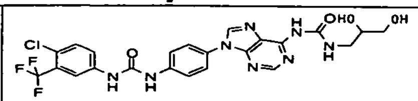
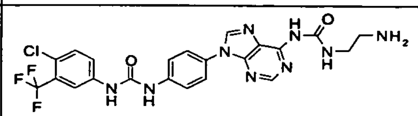
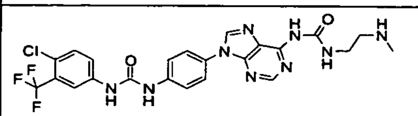
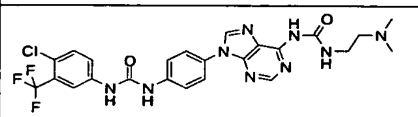
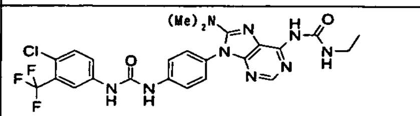
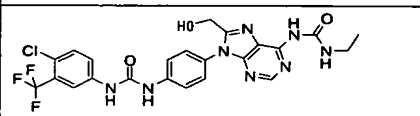
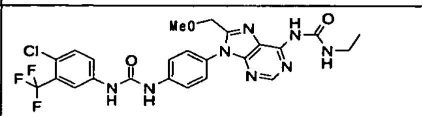
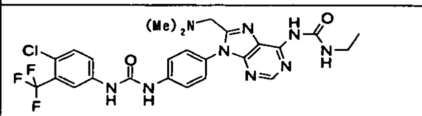
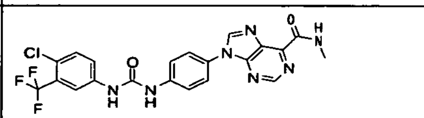
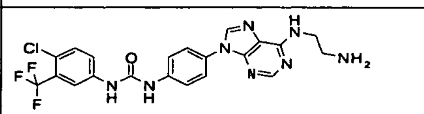
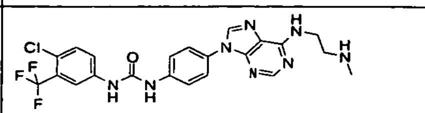
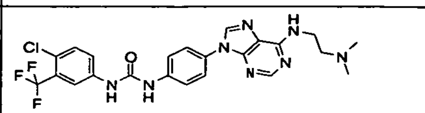
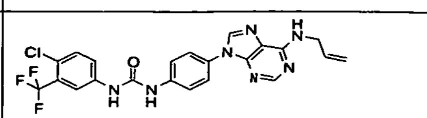
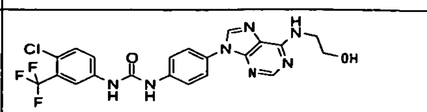
[0085]

[Table 1-10]

132		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1,3-dimethylurea	
133		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1,3,3-trimethylurea	
134		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethyl-1-methylurea	
135		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-methyl-3-propylurea	
136		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-isopropyl-1-methylurea	
137		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-hydroxyethyl)-3-methylurea	
138		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethyl-1-(2-hydroxyethyl)urea	
139		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-methoxyethyl)-3-methylurea	
140		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethyl-1-(2-methoxyethyl)urea	
141		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-dimethylaminoethyl)-3-methyl-urea	
142		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-dimethylaminoethyl)-3-ethyl-urea	
143		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-oxo-imdazolin-1-yl)purin-9-yl]-phenyl}urea	
144		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(3-methyl-2-oxo-imdazolin-1-yl)purin-9-yl]phenyl}urea	
145		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2-hydroxyethyl)urea	

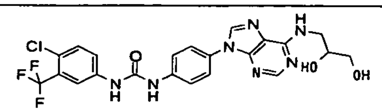
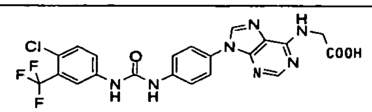
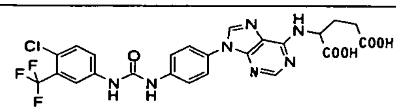
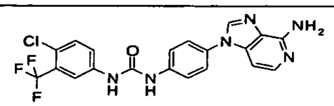
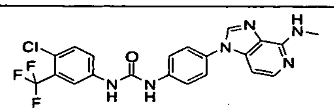
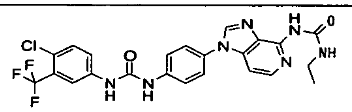
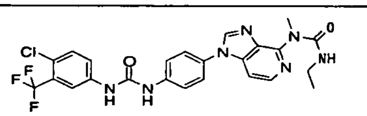
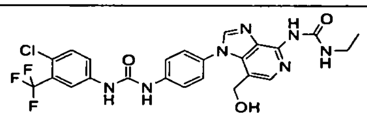
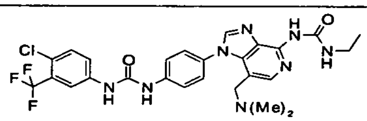
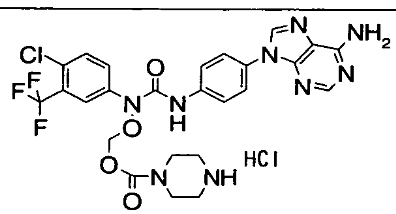
[0086]

[Table 1-11]

146		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2,3-dihydroxypropyl)urea	
147		1-(2-Aminoethyl)-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea	
148		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2-methylaminoethyl)urea	
149		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2-dimethylaminoethyl)urea	
150		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-8-dimethylamino-9H-purin-6-yl)-3-ethylurea	
151		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-8-hydroxymethyl-9H-purin-6-yl)-3-ethylurea	
152		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-8-methoxymethyl-9H-purin-6-yl)-3-ethylurea	
153		1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-8-dimethylaminomethyl-9H-purin-6-yl)-3-ethylurea	
154		9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purine-6-carboxylic acid methylamide	
155		1-{4-[6-(2-Amino-ethylamino)-purin-9-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea	
156		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-(6-(2-methylamino-ethylamino)purin-9-yl)phenyl}urea	
157		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-dimethylamino-ethylamino)-purin-9-yl]phenyl}urea	
158		1-[4-(6-Allylamino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea	
159		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-hydroxy-ethylamino)-purin-9-yl]phenyl}urea	

[0087]

[Table 1-12]

160		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2,3-dihydroxy-propylamino)-purin-9-yl]phenyl}urea	
161		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-ylamino)-acetic acid	
162		2-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-ylamino)-pentanedicarboxylic acid	
163		1-[4-(4-Aminoimidazo[4,5-c]-pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea	
164		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-[4-(4-methylamino-imidazo[4,5-c]-pyridin-1-yl)phenyl]urea	
165		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]-pyridin-4-yl}-3-ethylurea	
166		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]-pyridin-4-yl}-3-ethyl-1-methylurea	
167		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-7-hydroxymethyl-1H-imidazo[4,5-c]pyridin-4-yl}-3-ethyurea	
168		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-7-dimethylamino-methyl-1H-imidazo[4,5-c]- pyridin-4-yl)-3-ethylurea	
169		3-[4-[6-Aminopurin-9-yl]-phenyl]-1-(4-chloro-3-(tri-fluoromethylphenyl)11-(1-piperazinecarbonyloxy-methoxy)urea hydrochloride	

[0088]

The method for preparing the compound of the present invention will now be explained. Further, when the defined groups undergo an undesirable chemical conversion under the

conditions for carrying out the method in the preparation method as shown below, for example, by using means to protect and deprotect the functional groups, the preparation can be performed. Herein, as the selection of a protective group and the operation of deprotection, for example, the method as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (Second Edition, John Wiley & Sons, 1991)" can be mentioned, and this may be suitably used in accordance with reaction conditions. Further, if necessary or required, the order of the reaction step for introducing a substituent and the like may be changed. As the method for preparing the compound represented by formula (1), various methods can be thought and the compound can be synthesized by using the conventional organic synthesis means and, for example, the compound can be prepared by the following method as a representative method.

[0089]

Representative Preparation Method

Preparation Method 1

The compounds which are represented by formula (1) of the present invention can be prepared, for example, according to the following method but the method for preparing the compounds of the present invention is not limited thereto. The compounds of the present inventions are all novel compounds not described in literature but can be prepared by using known chemical techniques. Further, as the raw material compounds which are used in the

preparation, commercially available compounds may be used or the raw material may be prepared according to the conventional method, if necessary. Further, in Reaction Steps 1 to 4 and their explanation, R^1 to R^7, Q, Z^1, Z^2, W, Ra, Rb, Ra', Rb', Rc, Rc', Rd and Rd' mean the same as in defined in the above described formula (1). Further, L is an elimination group such as a halogen atom, a methane-sulfonyloxy group and a p-toluenesulfonyloxy group, and PG is a protective group such as a C_1-C_6 alkylcarbonyl group including an acetyl group, a C_1-C_6 alkoxycarbonyl group including t-butoxycarbonyl group, an aryl C_1-C_6 alkyl-carbonyl group including a benzyloxycarbonyl group and tri(C_1-C_6 alkyl)silyl group including t-butylmethylsilyl group.

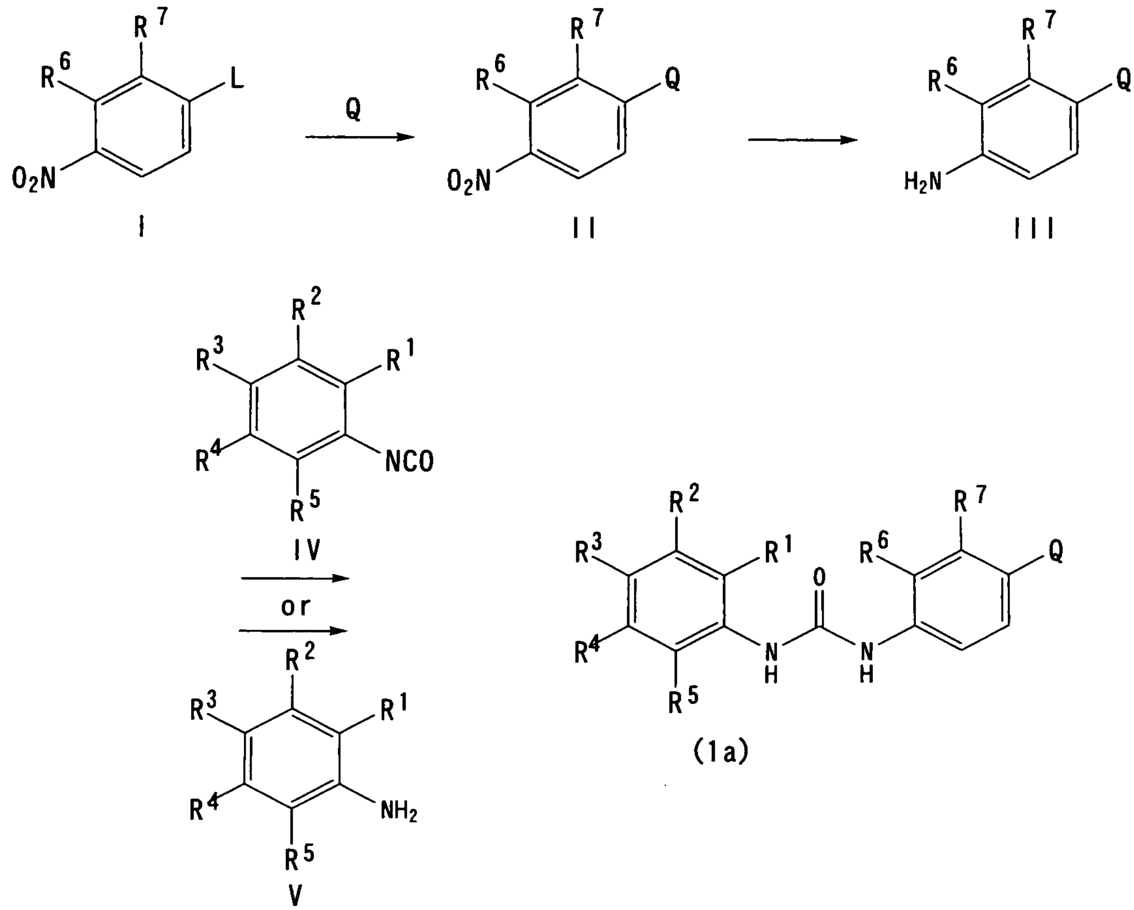
[0090]

1. General Method for Synthesizing Compound (1a) When Z^1 and Z^2 are Both H

Reaction Step 1

[0091]

[Formula 8]



[0092]

A 4-heteroaryl nitrobenzene derivative (II) can be prepared by the method as described in the known document [Ichikawa, J. et al., J. Org. Chem., Vol.61(8), 2763-2769, 1996] or a similar method. According to this method, a nitrobenzene derivative (I) can is allowed to react with a heteroaryl derivative Q in the presence of a suitable base (for example, sodium hydride, potassium carbonate or potassium butoxide) in a suitable solvent [for example, DMF (dimethylformamide) or DMSO (dimethyl sulfoxide)] to obtain a 4-heteroarylnitrobenzene derivative (II). The obtained

4-heteroarylnitrobenzene (II) is isolated and purified and then is reduced to a 4-heteroarylaniline derivative (III) by a known method (for example, catalytic reduction). By allowing the obtained 4-heteroarylaniline derivative (III) to react with an aryl isocyanate derivative (IV) in a suitable solvent (for example, dichloromethane or THF), a compound represented by formula (1a) can be obtained. The aryl isocyanate derivative (IV) is easily available by utilizing a commercially available reagent or by using the method as described in the known document [Knolker, H.J. et al., Angew. Chem. Int., Ed, Engl., Vol.34(22), 2497-2500, 1995] or a similar method. The compound (1a) can be prepared by using the method as described in the known documents [Nicolaou, K.C. et al., J. Am. Chem. Soc., Vol.122(12), 2966-2967, 2000; Macor, J.E. et al., Tetrahydron Lett., Vol.40(14), 2733-2736, 1999; and Kitterigham, J. et al., Synth. Commun., Vol.30 (11), 1937-1943, 2000] or a similar method. That is, the compound represented by formula (1a) can be obtained by allowing the 4-heteroarylaniline derivative (III) to react with an aniline derivative (V) in a suitable solvent [for example, dichloromethane, THF (tetrahydrofuran) or the like] in the presence of a urea bonding-forming reagent (for example, carbonyldiimidazole, phosgene, diphosgene, triphosgene or p-nitrophenyl chloroformate) and a base [for example, pyridine, trimethylamine or a Hunig's base (N,N-diiso-propylethylamine)]

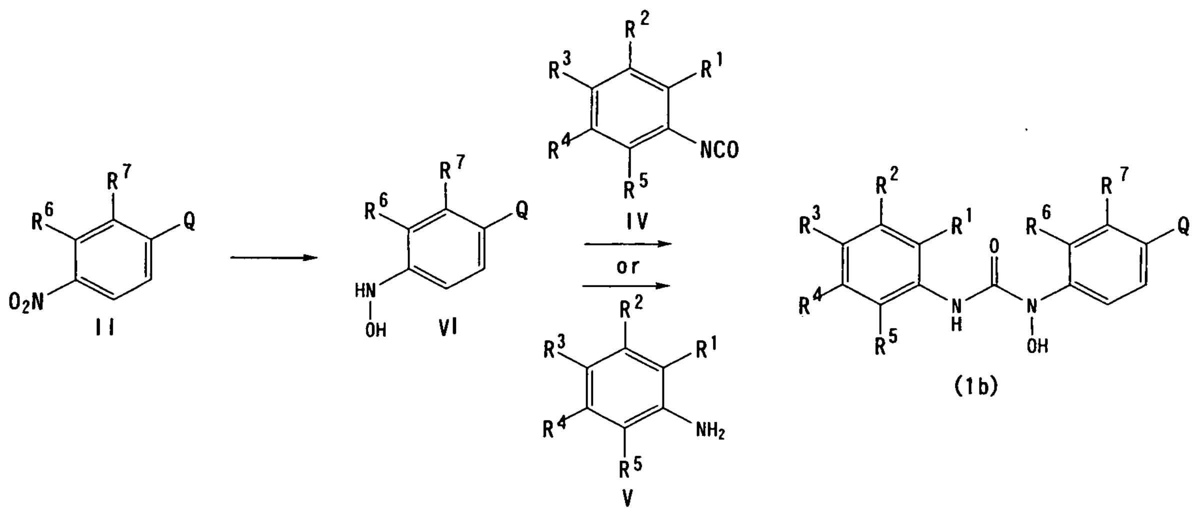
[0093]

2. General Method for Synthesizing Compound (1b) When Z^1 is H and Z^2 is OH

Reaction Step 2

[0094]

[Formula 9]



[0095]

In reaction step 2, the 4-heteroarylnitrobenzene derivative (II) obtained in Reaction Step 1 is isolated, purified and then is reduced to a 4-heteroarylphenyl-hydroxylamine derivative (VI) by using the known method as described in the known document (Panetta, C.A. et al., J. Org. Chem., Vol.34, 2773, 1969) or a similar method. By allowing the obtained 4-heteroarylphenylhydroxylamine derivative (VI) to react with the aryl isocyanate derivative (IV) in the same manner as in Reaction Step 1, a compound represented by formula (1b) can be obtained. Further, the compound represented by formula (1b) can be also prepared from the 4-heteroarylphenylhydroxylamine derivative (VI) and the aniline derivative (V) by using the

known method as described in the known documents [Nicolaou, K.C. et al., J. Am. Chem. Soc., Vol.122(12), 2966-2967, 2000; Macor, J. E. et al., Tetrahydron Lett., Vol.40(14), 2733-2736, 1999; and Kitterigham, J. et al., Synth. Commun., Vol.30(11), 1937-1943, 2000] or a similar method.

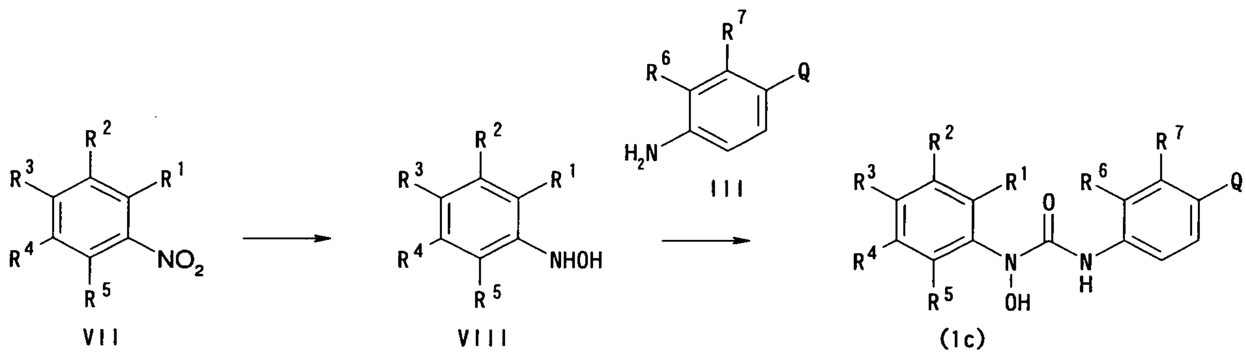
[0096]

3. General Method for Synthesizing Compound (1c) When Z^1 is OH and Z^2 is H

Reaction Step 3

[0097]

[Formula 10]



[0098]

A nitrobenzene derivative (VII) can be easily obtained by utilizing a commercially available reagent or by using the known method (for example, aromatic nitration reaction). The nitrobenzene derivative (VII) is reduced to a phenylhydroxylamine derivative (VIII) in the same manner as in Reaction Step 2. By allowing the obtained phenylhydroxylamine derivative (VIII) to react with the 4-heteroarylaniline derivative (III) obtained in Reaction Process 1 in the same manner as in reaction Step 2, a

compound represented by formula (1c) can be prepared.

[0099]

4. Functional Group Conversion of Substituent W on Heteroaryl Group Q

The compounds (1a) to (1c) in the Reaction Steps 1 to 3 can be further derivatized by the functional group conversion of a functional group W on the heteroaryl group with the use of known techniques of organic chemistry. By converting the same functional group in the starting material Q and in the stage (II) of an intermediate) in the Reaction Steps and then further performing the Reaction Steps 1 to 3, a derivative can also be obtained. On conversion of a functional group, if necessary, techniques of protection or deprotection with a suitable protective group (for example, acetyl, t-butoxy-carbonyl, benzyloxycarbonyl or t-butyldimethylsilyl) by the known method can be used.

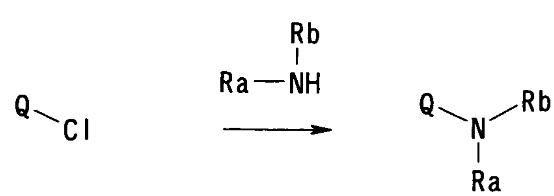
[0100]

As the representative example of functional group conversion used in the present invention, Reaction Processes 4-1 to 4-7 are given in a generalized form.

<u>Reaction Step 4-1</u>

[0101]

[Formula 11]



[0102]

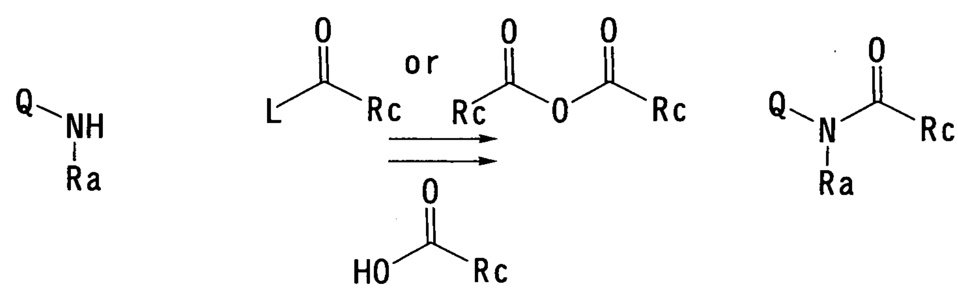
Reaction Step 4-1 is a reaction step of converting a chlorine on a heteroaryl group into an amino group. A target compound can be obtained by allowing a chloro-substituted heteroaryl compound to react with ammonia, a primary amine or a secondary amine in the absence of a solvent or in a suitable solvent (for example, methanol, ethanol or isopropanol).

[0103]

Reaction Step 4-2

[0104]

[Formula 12]



[0105]

Reaction Step 4-2 is a step of acylating an amino group on the heteroaryl group to obtain an amide derivative. A target compound can be obtained by reacting the amino substituted heteroaryl compound to react with a carboxylic acid halide or a carboxylic anhydride in the presence of a suitable base, for example, Hunig's base [N,N-diisopropylethylamine], triethylamine, pyridine or DMAP (dimethylaminopyridine)]. The target compound can be also prepared by allowing the amino substituted heteroaryl compound to react with a carboxylic acid together with a

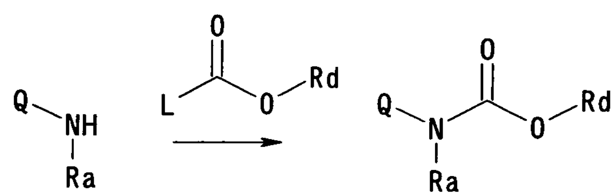
dehydration condensation agent and an auxiliary. As the dehydration condensation agent, HATU [(O-(7-azabenzo-triazol-1-yl)-N,N,N,N-tetra-methyluronium hexafluoro-phosphate), EEDQ (2-ethoxy-1-ethyoxycarbonyl-1,2-dihyroquinoline), PyBOP [(benzotriazolyloxytripyrroli-dino-phosphonium=hexafluorophosphate], PyBrOP [(bromotris-(pyrrolidino)-phosphonium=hexafluorophosphate], DDC (dicyclohexylcarbo-diimide), EDC (1-ethyl-3-(3,3'-dimethylaminopropylcarbodiimide) and the like can be mentioned. As the auxiliary, HOSu ((N-hydroxysuccinimide), HOAt (1-hydroxy-7-azabenzo-triazole), HOBt (1-hydroxy-benzotriazole) can be mentioned. As the base, trieethylamine, Hunig's base (N,N-diisopropylethylamine) or the like can be added.

[0106]

Reaction Step 4-3

[0107]

[Formula 13]



[0108]

Reaction Step 4-3 is a step of obtaining a carbamate derivative by oxycarbonylating an amino group on the heteroaryl group. A target compound can be obtained by allowing the amino substituted heteroaryl compound to react with an alkyl chloroformate in the presence of a suitable

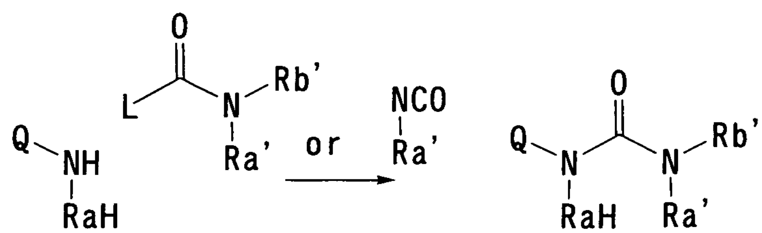
base [for example, Hunig's base (N,N-diisopropylethylamine), triethylamine, pyridine or DMAP (dimethylaminopyridine) or the like].

[0109]

Reaction Step 4-4

[0110]

[Formula 14]



[0111]

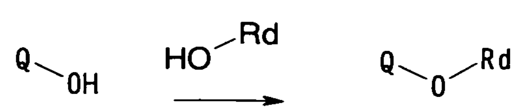
Reaction Step 4-4 is a step of obtaining a urea derivative by carbamoylating an amino group on the heteroaryl group. A target compound can be obtained by allowing the amino substituted heteroaryl compound to react with an carbamoyl chloride or an isocyanate in the presence of a suitable base [for example, Hunig's base (N,N-diisopropylethylamine), triethylamine, pyridine or DMAP (dimethylaminopyridine) or the like].

[0112]

Reaction Step 4-5

[0113]

[Formula 15]



[0114]

Reaction Step 4-5 is a step of obtaining an alkoxy

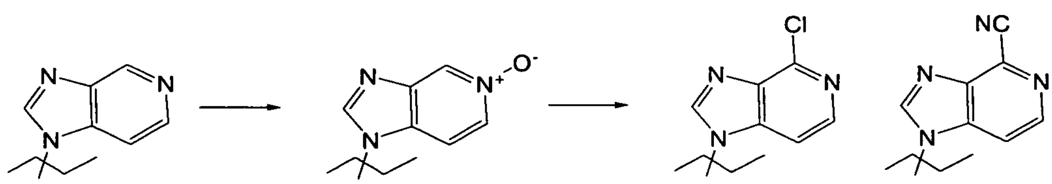
derivative by alkylating a hydroxyl group on the heteroaryl group. A target compound can be obtained byperforming the known Mitsunobu Reaction with the use of a heteroaryl compound substituted with a hydroxyl group and an alcohol corresponding to the hydroxyl group, that is, in any combination of a suitable phosphorus compound (for example, triphenylphosphine or tri-n-butylphosphine) with a suitable azo compound [for example, DEAD (diethyl azodicarboxylate) or TMAD (1,1'-azibis(N,N-dimethyl-formamide))].

[0115]

Reaction Step 4-6

[0116]

[Formula 16]



Q

etc.

[0117]

The reaction Step 4-6 is a step of introducing a chlorine atom, a cyano group or the like as a substituent W when the heteroaryl group Q is imidazo[4,5-c]pyridine. Imidazo[4,5-c] pyridine can be oxidized to imidazo[4,5-c] pyridine 5-oxide in a suitable acid solvent (for example, acetic acid) with the use of an suitable oxidizing agent (for example, hydrogen peroxide) in accordance with the method described in the known document (Mizuno, Y. et al., Chem. Pharm. Bull., Vol.12(8), 866-873, 1964) or a similar method. A nucleophile such as a chlorine atom, a cyano

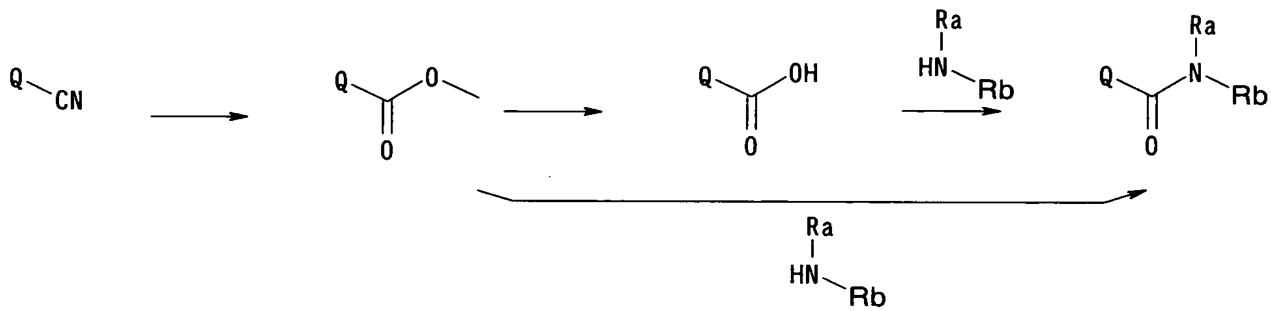
group or the like can be introduced into the imidazo[4,5-c]pyridine 5-oxide by using Reissert method or analogous methods described in the document (Hamana et al., Yakugaku Zasshi, Vol.120(2), 206-223, 2000) or a similar method.

[0118]

Reaction Step 4-7

[0119]

[Formula 17]



[0120]

Reaction Step 4-7 is a step of converting a cyano group on the heteroaryl group into a carboxamide through a carboxylate. By treating the cyano substituted heteroaryl compound in a suitable solvent (for example, methanol) with a suitable base (for example, sodium methylate) or an acid (for example, methanol hydrochloric acid), the cyano group can be converted to carboxylic acid methyl ester. By leading the carboxylic acid methyl ester to a carboxylic acid by hydrolysis and then allowing the carboxylic acid to react with the corresponding amine together with the dehydration condensation agent and the auxiliary as described in Reaction Step 4-2, the carboxamide can be prepared. The carboxamide derivative can be obtained in one

step by the exchange reaction of the carboxylic acid methyl ester derivative with the corresponding amine in a suitable solvent (for example, methanol).

[0121]

Synthesis of Raw Materials

Part of the raw materials of the compounds of the present invention are novel compounds and these compounds can be easily synthesized in the same manner as in synthesizing known raw materials or using known methods for a person with ordinary skill in the art.

[0122]

One example of the method for preparing the compounds of formula (1) relating to the present invention is shown above but the isolation/purification of the target compounds as shown in the above described Reaction Steps can be performed by applying normal chemical operations such as extraction, concentration, distillation, crystallization, filtration, recrystallization and various types of chromatographies.

[0123]

The compounds and their pharmaceutically acceptable salts of the present invention include all stereoisomers [for example, enantiomers and diastereomers (including cis- and trans-geometrical isomers)] of the compounds represented by formula (1), racemic bodies of the above described isomers and other mixtures of the above described isomers.

[0124]

Further, the compounds and their pharmaceutically acceptable salts of the present invention can exist in several tautomeric forms, for example, enol and imine forms, keto and enamine forms and their mixtures. The tautomers exist as a mixture of a tautomeric set in a solution, and one of the tautomers normally prevails in the form of a solid. The compounds of the present invention include all tautomers.

[0125]

When the compounds relating to the present invention are obtained in free-forms, they can be converted to salts hydrates or solvates which the compounds are allowed to form according to the conventional methods.

[0126]

Further, when the compounds relating to the present invention are obtained as the salts, hydrates or solvates of the compounds, they can be converted to the free forms of the compounds according to the conventional methods.

The compounds or their pharmaceutically acceptable salts relating to the present invention have excellent Ras inhibition and angiogenesis inhibition actions and excel in the internal stability and the solubility in water, and are useful as preventive or therapeutic agents (especially therapeutic agents) for the disease selected from cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes. Furthermore, the compounds of the present invention are useful as preventive or therapeutic agents (especially therapeutic agents) for the metastasis/

infiltration of a solid cancer.

[0127]

These methods include a step of administering a pharmaceutically effective amount of a pharmaceutical composition containing the compound or its pharmaceutically acceptable salt disclosed in the present invention to a patient who requires such a treatment or has such a disease or in such a state.

[0128]

When the pharmaceutical composition of the present invention is used as a therapeutic agent or a preventive for a disease selected from cancer, psoriasis, athero-sclerosis, chronic rheumatoid arthritis and diabetes, as the administration method, oral, rectal, parenteral (intravenous, intramuscular and subcutaneous), intracisternal, vaginal, intraabdominal, intravesical and topical (a drip, a powder, an ointment, a gel or a cream) administrations, inhalation (an oral cavity or nasal spray) and the like can be mentioned. As the administration form, for example, tablets, capsules, granules, powders, pills, aqueous or nonaqueous oral solutions or suspensions and parenteral solutions filled in containers suitable for subdivision into an each dose can be mentioned. Further, the administration form can be adjusted to various administration method including a releasably adjusted formulation such as subcutaneous implantation.

[0129]

The above described pharmaceutical preparations can

be prepared by the known method with the use of additives such as an excipient, a lubricant (a coating material), a binder, a disintegrator, a stabilizer, a corrective and a diluent.

As the excipient, for example, starch such as starch, potato starch and corn starch, lactose, crystalline cellulose, calcium hydrogenphosphate and the like can be mentioned.

[0130]

As the coating material, for example, ethyl cellulose, hyroxypropyl cellulose, hydroxypropylmethyl cellulose, shellac, talc, carnauba wax, paraffin and the like can be mentioned.

[0131]

As the binder, for example, polyvinylpyrrolidone, macrogol and the same compounds as the excipients can be mentioned.

As the disintegrator, for example, the same compounds as the excipients and chemically modified starch/ celluloses such as cross calmellose sodium, carboxymethyl starch sodium and crosslinked polyvinylpyrrolidone can be mentioned.

[0132]

As the stabilizer, for example, p-hydoxybenzoic acid esters such as methylparaben and propylparaben; alchohols such chlorobutanol, benzyl alcohol and phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid.

[0133]

As the corrective, for example, a sweet taste, an acid taste, a flavor and the like which are conventionally used can be mentioned.

Further, as a solvent for preparing a liquid and a solution, for example, ethanol, phenol, chlorocresol, purified water, distilled water and the like can be used.

[0134]

As the surface active agent or an emulsifier, for example, polysorbate 80, polyoxyl 40 stearate, lauromacgol and the like can be mentioned.

When the pharmaceutical composition of the present invention is used as a therapeutic or preventive agent for a disease selected from cancer, psoriasis, athero-sclerosis, chronic rheumatoid arthritis and diabetes, the amount of use of the compound or its pharmaceutically acceptable salt of the present invention varies depending on the state of a disease, age, body weight, relative state of health, the presence or absence of other medications, the method of administration and the like. For example, for a patient (a warm-blooded animal, particularly a human), a typical daily effective dose as an active ingredient (the compound represented by formula (1) of the present invention) for an oral medicine is preferably 0.1 to 1,000 mg/kg of body weight, more preferably 0.1 to 400 mg/kg of body weight. The daily dose for the normal weight of an adult patient is preferably in the range of 10 to 800 mg. For an parenteral medicine, the daily dose is preferably 0.1 to 1,000 mg/kg

of body weight, more preferably 10 to 800 mg/kg of body weight. It is preferred that these doses are administered at one time a day or in divisions at several times in according to the state of the disease.

[Effect of The Invention]

[0135]

According to the present invention, a preventive or a therapeutic agent (particularly a therapeutic agent) which not only has the existing Raf inhibition and angiogenesis inhibition actions but also excels in the solubility in water to show highly stable oral bioavailability and excels in the safety for proliferative diseases is provided. Further, according to the present invention, a compound useful for therapeutic and preventive agent effective for proliferative diseases such as cancer and cancerous metastasis, its production method, an intermediate useful for its production, and furthermore a pharmaceutical composition comprising these compounds are provided.

[Examples]

[0136]

The present invention will be explained in more detail by examples but the present invention is not limited to these examples.

Further, the NMR analysis was performed by using JEOL JNM-EX 270 (270 MHz) or JNM GSX 400 (400 MHz), and the NMR data were shown by ppm (parts per million: δ) and the deuterium lock signal for a sample solvent was referred to. The mass spectral data were obtained by using JEOL JMS-DX

300 or JMS-SX/SX 102 or with the use of Finnigan micromass Navigator equipped with Agilent Technologies Agilent 100 gradient HPLC. The specific rotation was measured with the use of sodium D-line at room temperature.

[0137]

In the organic synthesis reactions, commercially available reagents were used without further purification. The term "room temperature" refers to a range of about 20 to 25°C. All water prohibitive reactions were performed with the use of a rotary evaporator unless expressly stated.

[0138]

In preparing the compounds, if necessary, a functional group was protected with a protective group and after preparation of the protected target compound, the protective group was removed. The selection of protective groups and the operation of deprotection were performed, for example, according to the method described in Greene and Wuts, "Protective Groups in Organic Synthesis" (Second Edition, John Wiley & Sons, 1991)".

[Example 1]

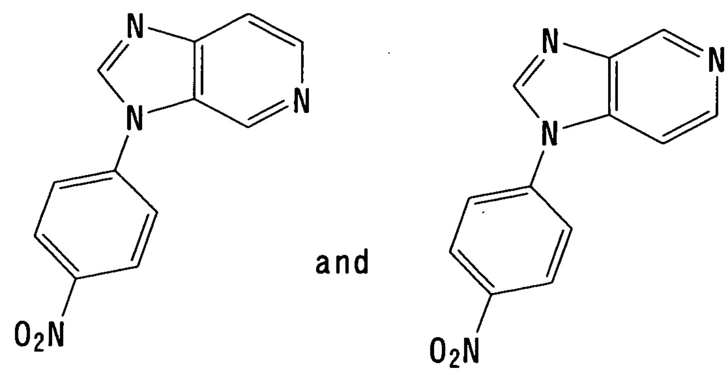
Synthesis of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 1)

Step A

Preparation of 3-(4-nitorphenyl)-3H-imidazo[4,5-c]-pyridineand 1-(4-nitrophenyl)1H-imidazo[4,5-c]pyridine

[0139]

[Formula 18]



[0140]

In 3 mL of dimethylformamide, 119 mg (1.00 mmol) of imidazo[4,5-c]pyridine was dissolved, and 138 mg (1.00 mmol) of potassium carbonate and 141 mg (1.00 mmol) of 4-fluoronitrobenzene were added thereto and the mixture solution was stirred at 80°C for two hours. The solution was diluted with 10 mL of water, and the formed precipitate was collected by filtration, washed with water, and vacuum dried. The obtained crude product was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol= 15:1) to obtain 18.9 mg (8%) of 3-(4-nitrophenyl)-3H-imidazo[4,5-c]pyridine and 66.6 mg (28%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine as yellow solids, respectively.

[0141]

3-(4-Nitrophenyl)-3H-imidazo[4,5-c]pyridine

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 7.77(2H,d,J=9.9 Hz), 7.82(1H,dd,J=1.0, 5.6 Hz), 8.30(1H,s), 8.51(2H,d,J=9.9 Hz), 8.59(1H,dd,J=1.0, 5.6 Hz), 9.03(1H,s)

1-(4-Nitrophenyl)-1H-imidazo[4,5-c]pyridine

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 7.51(1H,dd,J=1.0, 5.6

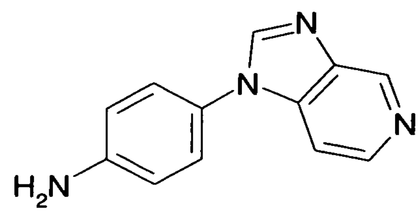
Hz), 7.72(2H,d,J=9.9 Hz), 8.23(1H,s), 8.50(2H,d,J=9.9 Hz), 8.59(1H,dd,J=1.0, 5.6 HZ), 9.24(1H,s)

Step B

Preparation of 4-(imidazo[4,5-c]pyridin-1-yl)aniline

[0142]

[Formula 19]



[0143]

In 20 mL of methanol, 33 mg (0.1237 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine prepared in Step A was dissolved and the solution was stirred on 5 mg of 10% palladium carbon in a hydrogen atmosphere at room temperature at normal pressures for one hour. After removal of the palladium carbon by filtration, the solvent was distilled under reduced pressure, and the obtained product was vacuum dried to obtain 4-(imidazo[4,5-c]-pyridin-1-yl)aniline as a white solid. This product was used in process C without further purification.

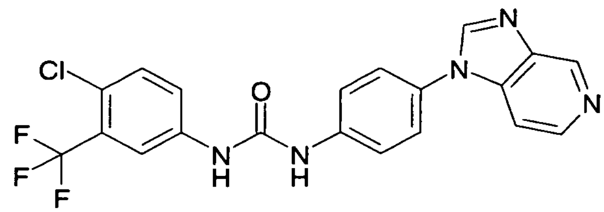
[0144]

Step C

Preparation of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 1)

[0145]

[Formula 20]



[0146]

The 4-(imidazo[4,5-c]pyridin-1-yl)aniline prepared in Step B was dissolved in 10 mL of dichloromethane, and 30 mg (0.137 mmol) of 4-chloro-3-(trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for three hours. The solvent was distilled under reduce pressure, and the obtained crude product was recrystallized from ethyl acetate to obtain 35.0 mg (51%) of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 1) as a colorless crystal.

[0147]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.62-7.76(7H,m), 8.14(1H,d,J=2.0 Hz), 8.43(1H,d,J=5.6 Hz), 8.70(1H,s), 9.09(1H,s), 9.18(1H,s), 9.28(1H,s) ESI (LC-MS positive mode) m/z 431.9 (M+H)

[Example 2]

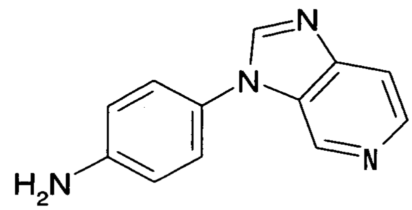
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-c]pyridin-3-ylphenyl)urea (Table 1, Compound No. 2)

Step A

Preparation of 4-(imidazo[4,5-c]pyridin-3-yl)aniline

[0148]

[Formula 21]



[0149]

In 10 mL of methanol, 15.9 mg (0.066 mmol) of 4-nitrophenyl-3H-imidazo[4,5-c]pyridine prepared in Step A of Example 1 was dissolved and the solution was stirred on 5 mg of 10% palladium carbon in a hydrogen atmosphere at room temperature at normal pressures for one hour. After removal of the palladium carbon by filtration, the solvent was distilled under reduced pressure, and the residue was vacuum dried to obtain 4-(imidazo[4,5-c]pyridin-3-yl)-aniline as a white solid. The product was used in Step B without further purification.

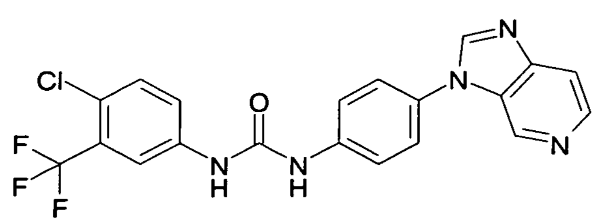
[0150]

Step B

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-imidazo[4,5-c]pyridin-3-ylphenyl)urea (Table 1, Compound No. 2)

[0151]

[Formula 22]



[0152]

The 4-(imidazo[4,5-c]pyridin-3-yl)aniline prepared in

Step A was dissolved in 10 mL of dichloromethane, and 14.2 mg (0.064 mmol) of 4-chloro-3-(trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for three hours. The solvent was distilled under reduced pressure, and the obtained crude product was recrystallized from ethyl acetate to obtain 20.2 g (73%) of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-imidazo[4,5-c]pyridin-3-ylphenyl)urea (Table 1, Compound No. 2) as a colorless crystal.

[0153]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.63-7.80(7H,m), 8.14(1H,d,J=2.0 Hz), 8.43(1H,d,J=5.6 Hz), 8.77(1H,s), 8.98(1H,s), 9.18(1H,s), 9.28(1H,s), 9.29(1H,s)

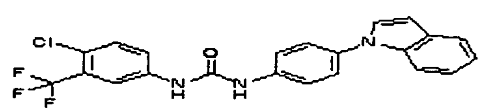
ESI (LC-MS positive mode) m/z 431.9 (M+H)

[Example 3]

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-indol-1-ylphenyl)urea (Table 1, Compound No. 3)

[0154]

[Formula 23]



[0155]

The titled compound can be synthesized from indole, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by using the same techniques as in Example 1.

[0156]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.68(1H,d,J=3.3 Hz), 7.03-7.20(7H,m), 7.50(2H,d,J=8.6 Hz), 7.60-7.70(7H,m), 8.14(1H,d,J=1.0 Hz), 9.06(1H,s), 9.24(1H,s)

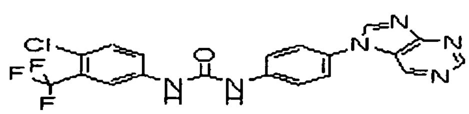
ESI (LC-MS positive mode) m/z 431.9 (M+H)

[Example 4]

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-purin-7-ylphenyl)urea (Table 1, Compound No. 4)

[0157]

[Formula 24]



[0158]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0159]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.62-7.67(3H,m), 7.73(3H,s), 8.12(1H,m), 9.08(2H,d,J=5.3 Hz), 9.21(1H,s), 9.36(1H,s), 9.50 (1H,s)

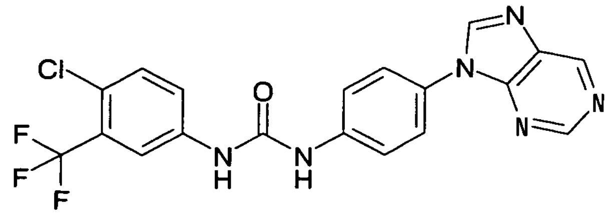
ESI (LC-MS positive mode) m/z 433 (M+H)

[Example 5]

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-purin-9-ylphenyl)urea (Table 1, Compound No. 5)

[0160]

[Formula 25]



[0161]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0162]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.63(2H,m), 7.85(4H,dd,J=23.8, 11.8 Hz), 8.08(1H,d,J=3.7 Hz), 8.39(1H,s), 9.02(1H,s), 9.17(1H,s), 9.28(1H,s), 9.30(1H,s)

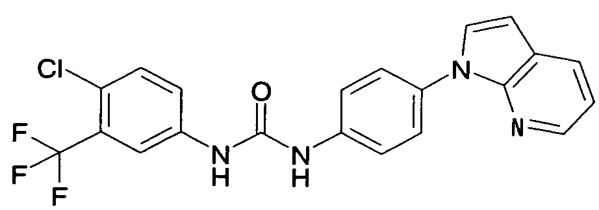
ESI (LC-MS positive mode) m/z 433 (M+H)

[Example 6]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-pyrrolo-[2,3-b]pyridin-1-ylphenyl)urea (Table 1, Compound No.6)

[0163]

[Formula 26]



[0164]

The title compound can be synthesized from pyrrolo[2,3-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same

techniques as in Example 1.

[0165]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.70 (1H,d,J=3.6 Hz), 7.19(1H,dd,J=7.9, 4.8 Hz), 7.58-7.66(4H,m), 7.80(2H,d,J=8.9 Hz), 7.89(1H,d,J=3.7 Hz), 8.04-8.13(2H,m), 8.30(1H,s), 9.02(1H,s), 9.22(1H,s)

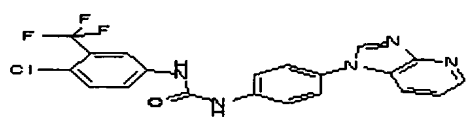
ESI (LC-MS positive mode) m/z 431 (M+H)

[Example 7]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-b]pyridin-1-ylphenyl)urea (Table 1, Compound No. 7)

[0166]

[Formula 27]



[0167]

The title compound can be synthesized from imidazo[4,5-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0168]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.39(1H,dd,J=4.6, 7.9 Hz), 7.60-7.70(4H,m), 7.85(2H,d,J=8.9 Hz), 8.13(1H,m), 8.20(1H,m), 8.43(2H,m), 8.85(1H,s), 9.11(1H,s), 9.25(1H,s)

ESI (LC-MS positive mode) m/z 432 (M+H)

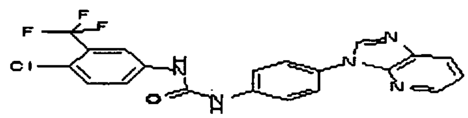
[Example 8]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-

[4,5-b]pyridin-3-ylphenyl)urea (Table 1, Compound No. 8)

[0169]

[Formula 28]



[0170]

The title compound can be synthesized from imidazo[4,5-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0171]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.37(1H,dd,J=4.9, 8.2 Hz), 7.60-7.75(6H,m), 8.05(1H,dd,J=1.3, 7.9 Hz), 8.14(1H,d,J=2.3 Hz), 8.51(1H,dd,J=1.7, 5.0 Hz), 8.81(1H,s), 9.17(1H,s), 9.28(1H,s)

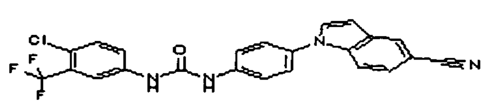
ESI (LC-MS positive mode) m/z 432 (M+H)

[Example 9]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cyanoindol-1-yl)phenyl]urea (Table 1, Compound No. 9)

[0172]

[Formula 29]



[0173]

The title compound can be synthesized from 5-cyanoindole, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same

techniques as in Example 1.

[0174]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.85(1H,d,J=3.3 Hz), 7.50-7.56(3H,m), 7.60-7.72(5H,m), 7.83(1H,d,J=3.3 Hz), 8.13(1H,d,J=2.3 Hz), 8.21(1H,d,J=0.7 Hz), 9.12(1H,s), 9.24(1H,s)

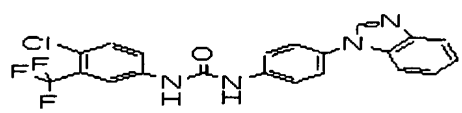
ESI (LC-MS positive mode) m/z 455 (M+H)

Example 10

1-(4-Benzimdazol-1-ylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (Table 1, Compound No. 10)

[0175]

[Formula 30]



[0176]

The title compound can be synthesized from benzimidazole, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0177]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.28-7.33(2H,m), 7.55-7.80(8H,m), 8.14(1H,d,J=0.8 Hz), 8.51(1H,s), 9.14(1H,s), 9.28(1H,s)

ESI (LC-MS positive mode) m/z 431 (M+H)

[Example 11]

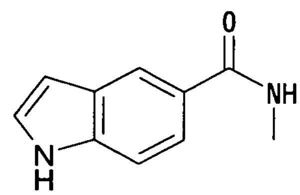
1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indole-5-carboxylic acid methylamide (Table 1, Compound No. 11)

Step A

Preparation of 1H-indole-5-carboxylic acid methylamide

[0178]

[Formula 31]



[0179]

In 5 mL of N,N-dimethylformamide, 500 mg (3.1 mmol) of 1H-indole-5-carboxylic acid, 750 mg (9.3 mmol) of 40% methylamine, 477 mg (3.1 mmol) of benzotriazole-1-ol hydrate and 713 mg (3.8 mmol) of (3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride were dissolved and the solution was stirred at room temperature for three hours, and then the solvent was distilled under reduced pressure. The obtained residue was dissolved in ethyl acetate and washed with a saturated sodium hydrogencarbonate solution (50 mL, twice) and a saturated saline (50 mL) in the order named. The organic layer was dried and then concentrated to obtain 397 mg (73%) of a crude product of 1H-indole-5-carboxylic acid methylamide. The product was used in the next reaction without further purification.

[0180]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.01(3H,d,J=4.9 Hz), 6.20(1H,br.s), 6.59(1H,br.s), 7.20-7.22(2H,m), 7.37(1H,d,J=8.6 Hz), 7.60(1H,d,J=8.6 Hz), 8.07(1H,s), 8.64(1H,br.s),

ESI (LC-MS positive mode) m/z 175 (M+H)

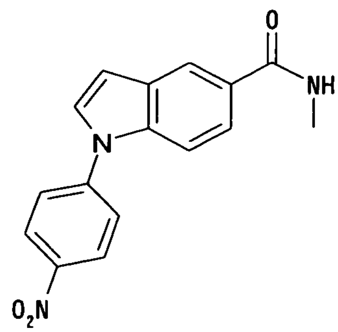
[0181]

Step B

Preparation of 1-(4-nitrophenyl)-1H-insole-5-carboxylic acid methylamide

[0182]

[Formula 32]



[0183]

The title compound can be synthesized from 1H-indole-5-carboxylic acid methylamide and 4-fluoronitro-benzene in the same manner as in Step A of Example 1.

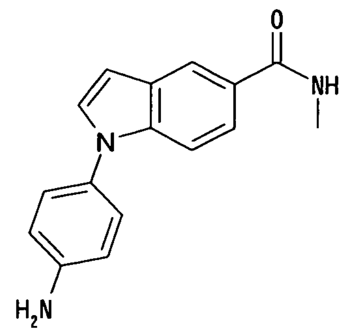
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.84(3H,d,J=4.8 Hz), 6.93(1H,d,J=3.3 Hz), 7.80(2H,s), 7.90-8.00(3H,m), 8.24(1H,s), 8.42-8.50(3H,m)

Step C

Preparation of 1-(4-aminophenyl)-1H-indole-5-carboxylic acid methylamide

[0184]

[Formula 33]



[0185]

The title compound can be synthesized from 1-(4-nitrophenyl)-1H-indole-5-carboxylic acid methylamide in the same manner as in Step B of Example 1.

^{1}H-NMR (270 MHz, CD_3OD) δ (ppm): 2.95(3H,d,J=4.8 Hz), 6.78(1H,d,J=3.3 Hz), 6.86(2H,d,J=9.6 Hz), 7.21(2H,d,J=9.6 Hz), 7.38-7.41(2H,m), 7.62(1H,dd,J=1.6, 8.5 Hz), 8.13(1H,d,J=1.3 Hz), 8.34(1H,br.s),

ESI (LC-MS positive mode) m/z 266 (M+H)

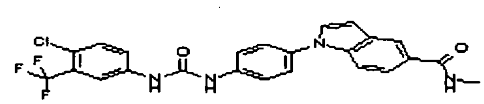
[0186]

Step D

Preparation of 1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-indole-5-carboxylic acid methylamide (Table 1, Compound No. 11)

[0187]

[Formula 34]



[0188]

The title compound can be synthesized from 1-(4-aminophenyl)-1H-indole-5-carboxylic acid methylamide and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same

manner as in Step C in Example 1.

[0189]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.81(3H,d,J=4.3 Hz), 6.79 (1H,d,J=3.3 Hz), 7.50-7.55(3H,m), 7.63-7.75(6H,m), 8.14(1H,d,J=2.0 Hz), 8.20(1H,d,J=0.7 Hz), 8.38(1H,q,J=4.3 Hz), 9.09(1H,s), 9.24(1H,s)

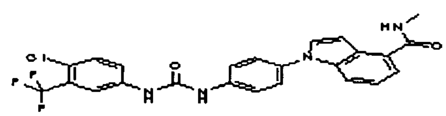
ESI (LC-MS positive mode) m/z 487 (M+H)

[Example 12]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indole-4-carboxylic acid methylamide (Table 1, Compound No. 12)

[0190]

[Formula 35]



[0191]

The title compound can be synthesized from 1H-indole-4-carboxylic acid, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0192]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.84(3H,d,J=4.3 Hz), 7.09 (1H,d,J=3.3 Hz), 7.23(1H,dd,J=8.3, 7.6 Hz), 7.47-7.53(3H,m), 7.60-7.75(6H,m), 8.14(1H,d,J=2.0 Hz), 8.29(1H,t,J=4.3 Hz), 9.08(1H,s), 9.24(1H,s)

ESI (LC-MS positive mode) m/z 487.2 (M+H)

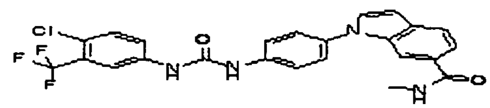
[Example 13]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-

phenyl}-1H-indole-6-carboxylic acid methylamide (Table 1, Compound No. 13)

[0193]

[Formula 36]



[0194]

The title compound can be synthesized from 1H-indole-6-carboxylic acid, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0195]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.88(3H,d,J=4.3 Hz), 6.73(1H,d,J=3.0 Hz), 7.55(2H,d,J=8.9 Hz), 7.60-7.76(7H,m), 8.00(1H,s), 8.14(1H,d,J=2.3 Hz), 8.40(1H,t,J=4.3 Hz), 9.10(1H,s), 9.26(1H,s)

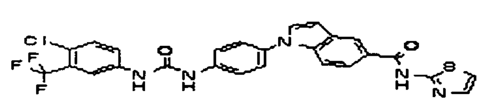
ESI (LC-MS positive mode) m/z 487.0 (M+H)

[Example 14]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indole-5-carboxylic acid thiazol-2-ylamide (Table 1, Compound No. 14)

[0196]

[Formula 37]



[0197]

The title compound can be synthesized from 1H-indole-4-carboxylic acid, 4-fluoronitrobenzene, 2-aminothiazole

and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0198]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.52(1H,s), 7.12(1H,d,J=4.3 Hz), 7.39-7.40(2H,m), 7.60-7.75(7H,m), 7.85(1H,d,J=8.6 Hz), 8.16(1H,s), 8.31(1H,s), 9.23(1H,s), 9.39(1H,s), 11.30(1H,s)

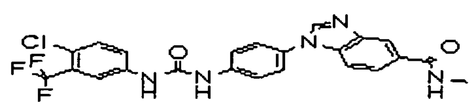
ESI (LC-MS positive mode) m/z 556 (M+H)

[Example 15]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-benzimidazole-5-carboxylic acid methylamide (Table 1, Compound No. 15)

[0199]

[Formula 38]



[0200]

The title compound can be synthesized from 1H-benzimdazole-5-carboxylic acid, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0201]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.82(3H,d,J=2.7 Hz), 7.76-7.90(8H,m), 8.17(1H,br.d, J=1.0 Hz), 8.30(1H,s), 8.50(1H,br.s), 8.61(1H,s), 9.45(1H,br.s), 9.60(1H,br.s)

ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 16]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-2-

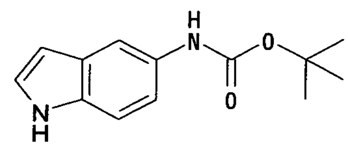
fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 16)

Step A

Preparation of (1H-indole-5-yl)carbamic acid tert-Butyl ester

[0202]

[Formula 39]



[0203]

In 100 mL of methanol, 2.64 g (20 mmol) of 5-aminoindole was dissolved, and 4.15 mL (30 mmol) of triethylamine and 5.23 g (24 mmol) of Boc_2O were added thereto and the mixture solution was stirred at room temperature for six hours. The reaction solution was concentrated under reduced pressure, and the residue was distributed with ethyl acetate (200 mL) and water (100 mL), and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the residue was distributed between ethyl acetate (200 mL) and water (100 mL) and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the residue was purified by a silica gel column (Wako Gel C200: 300 g, n-hexane:ethyl acetate=4:1) to obtain 4.38 g (94%) of (1H-

indol-5-yl)carbamic acid tert-butyl ester as a white solid.

[0204]

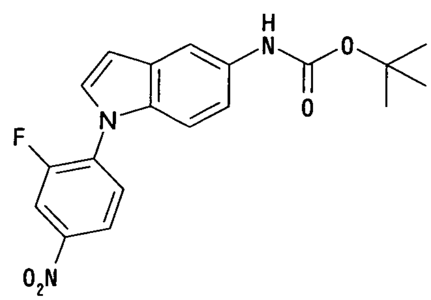
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.43(9H,s), 6.38(1H,br.s), 6.29-6.33(1H,m), 7.04(1H,dd,J=2.3, 8.9 Hz), 7.19(1H,s), 7.23(1H,d,J=8.9 Hz), 7.61(1H,br.s)

Step B

Preparation of [1-(2-fluoro-4-nitrophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester

[0205]

[Formula 40]



[0206]

The title compound can be synthesized from (1H-indol-5-yl)carbamic acid tert-butyl ester and 3,4-difluoro-nitroenzene in the same manner as in Step A of Example 1.

[0207]

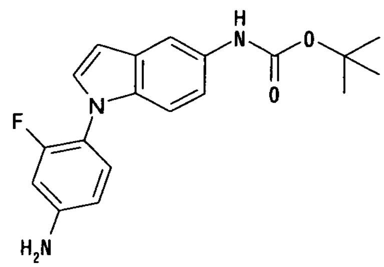
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.49(9H,s), 6.74(1H,d,J=3.3 Hz), 7.29 (2H,s), 7.62(1H,t,J=3.3 Hz), 7.82(1H,br.s), 7.96(1H,dd,J=8.6, 8.7 Hz), 8.23-8.29(1H,m), 9.23 (1H,s), 9.26(1H,br.s)

Step C

Preparation of [1-(4-amino-2-fluorophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester

[0208]

[Formula 41]



[0209]

The title compound can be synthesized from [1-(2-fluoro-4-nitrophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester in the same manner as in step B of Example 1.

[0210]

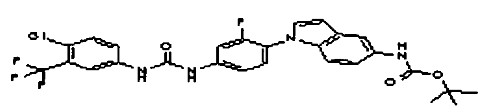
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.49(9H,s), 6.40-6.58(4H,m), 7.04-7.20(4H,m), 7.69(1H,br.s)

Step D

Preparation of 1-{4-[3-(4-Chloro-3-(trifluoromethyl-phenyl)ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 16)

[0211]

[Formula 42]



[0212]

The title compound can be synthesized from [1-(4-amino—2-fluorophenyl)-1H-indol-5-yl)carbamic acid tert-butyl ester and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Step C of Example 1.

[0213]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.58(9H,s),

6.60(1H,d,J=3.3 Hz), 7.60(1H, d, J=8.9 Hz),
7.21(1H,d,J=0.8 Hz), 7.34(1H,dd,J=0.8, 9.2 Hz),
7.42-7.54(2H,m), 7.62-7.78(4H,m), 8.12(1H,d,J=1.3 Hz),
9.18(1H,s), 9.28(1H,s), 9.33(1H,s)

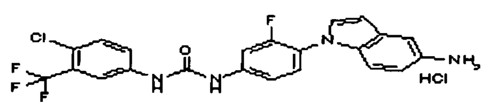
ESI (LC-MS positive mode) m/z 563.0 (M+H)

[Example 17]

1-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 17)

[0214]

[Formula 43]



[0215]

In 2 mL of ethyl acetate, 104 mg (0.18 mmol) of (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester was dissolved, and 2 mL of a 4N hydrogen chloride ethyl acetate solution was added thereto and the mixture solution was stirred at room temperature for one hour. The reaction solution was concentrated and the obtained product was triturated with ethyl acetate to obtain 80 mg (86%) of 1-[4-(5-aminoindol-1-yl)-3-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 17).

[0216]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.80(1H,d,J=2.6 Hz),
7.17(1H, d, J=8.9 Hz), 7.29(1H,d,J=8.9 Hz),

7.34(1H,d,J=9.2 Hz), 7.55(1H,t,J=8.9 Hz), 7.67(4H,m), 7.78(1H,d,J=13.2 Hz), 8.14(1H,s), 9.74(1H,br.s), 9.78(1H, br.s), 10.00(2H,br.s)

ESI (LC-MS positive mode) m/z 463.2 (M+H)

[Example 18]

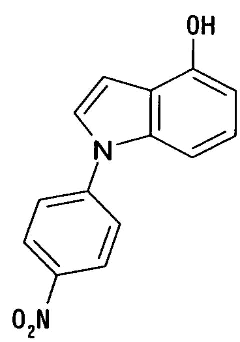
Acetic acid 1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-indol-4-yl ester (Table 1, Compound No. 18)

Step A

Preparation of 1-(4-nitrophenyl)-1H-indole-4-ol

[0217]

[Formula 44]



[0218]

The title compound can be synthesized from 1H-indole-4-ol and 4-fluoronitrobenze in the same manner as in Step A of Example 1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.11-6.14(1H,m), 6.82(1H,dd,J=0.7, 7.6 Hz), 6.59(1H,br.s), 7.06-7.10(2H,m), 7.16(1H,t,J=7.9 Hz), 7.34-7.38(2H,m), 8.20-8.28(2H,m), 11.45(1H,br.s)

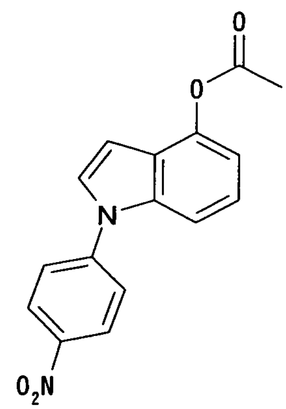
Step B

Preparation of Acetic acid 1-(4-nitrophenyl)-1H-

indol-4-yl ester

[0219]

[Formula 45]



[0220]

In 8 mL of methylene chloride, 387 mg (1.52 mmol) of 1-(4-nitrophenyl)-1H-indole-4-ol was dissolved, and 0.186 mL (2.00 mmol) of acetic anhydride and 0.318 mL (2.28 mmol) of triethylamine were added thereto and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was distributed between methylene chloride (50 mL) and a saturated ammonium chloride aqueous solution (20 mL) and washed with a saturated sodium chloride solution, and the organic layer was dried and then concentrated under reduced pressure to obtain acetic acid 1-(4- nitrophenyl)-1H-indol-4-yl ester. The product was used in the next reaction without further purification.

[0221]

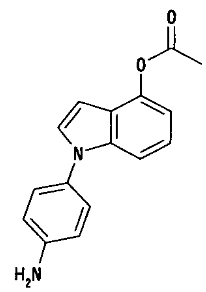
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 2.66(3H,s), 6.47-6.49(1H,m), 6.97-7.07(3H,m), 7.16-7.41(3H,m), 8.12-8.22(2H,m), 8.37(1H,d,J=8.6 Hz)

<u>Step C</u>

Preparation of acetic acid 1-(4-aminophenyl)-1H-indol-4-yl ester

[0222]

[Formula 46]



[0223]

The title compound can be synthesized from acetic acid 1-(4-nitrophenyl)-1H-indol-4-yl ester in the same manner as in Step B of Example 1.

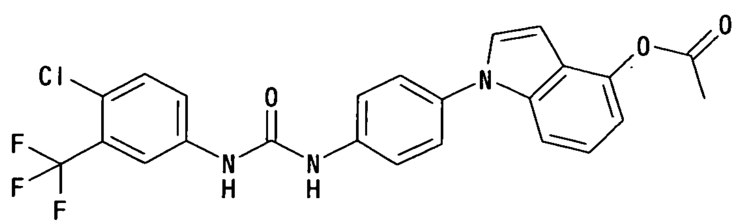
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 2.65(3H,s), 3.59(2H,s), 6.65-6.71(5H,m), 7.05-7.16(1H,m), 7.20(1H,d,J=3.2 Hz), 7.35(1H,d,J=2.7 Hz), 8.12(1H,d,J=5.5 Hz)

Step D

Preparation of acetic acid 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indol-4-yl ester

[0224]

[Formula 47]



[0225]

The title compound can be synthesized from acetic

acid 1-(4-aminophenyl)-1H-indol-4-yl ester and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Step C of Example 1.

[0226]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.66(3H,s), 6.60(1H,d,J=3.5 Hz), 6.75(1H, d, J=8.1 Hz), 6.99(2H,d,J=8.9 Hz), 7.28(1H,t,J=8.3 Hz), 7.45(2H,d,J=8.9 Hz), 7.60(2H,m), 7.82(1H,d,J=4.1 Hz), 8.11(2H,m), 8.82(1H,s), 9.12(1H,s)

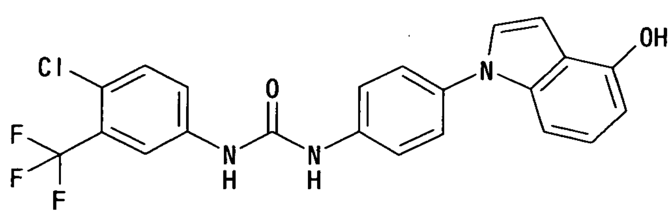
ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 19]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-hydroxyindol-1-yl)phenyl]urea (Table 1, Compound No. 19)

[0227]

[Formula 48]



[0228]

In 3 mL of tetrahydrofuran, 60 mg (0.12 mmol) of acetic acid 1-{4-[3-(4-chloro-3-(trifluoromthyl)phenyl)-ureido]phenyl}-1H-indol-4-yl ester was dissolved, and 1 mL of a 1N sodium hydroxide aqueous solution was added thereto and the mixture solution was stirred at room temperature for two hours. The reaction solution was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The

organic layer was washed with a saturated sodium chloride solution, dried and then concentrated under reduced pressure, and the obtained residue was recrystallized from ethyl acetate to obtain 17 mg (31%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-hydroxyindol-1-yl)phenyl]urea (Table 1, Compound No. 19) as a white solid.

[0229]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.21(1H,br), 6.48(1H,d,J=8.1 Hz), 6.63(1H,s), 6.89(4H,s), 6.95-7.02(2H,m), 7.05(1H,d,J=8.0 Hz), 7.19 (1H,d,J=8.9 Hz), 7.25(1H,t,J=3.0 Hz), 7.43(2H,d,J=8.6 Hz), 8.11(1H,s), 9.12(1H,s), 11.24(1H,s)

ESI (LC-MS positive mode) m/z 446 (M+H)

[Example 20]

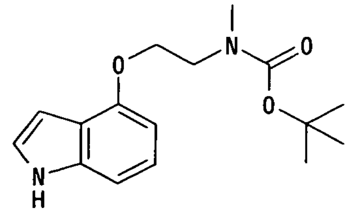
[2-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester (Table 1, Compound No. 20)

Step A

Preparation of [2-(1H-indol-4-yloxy)ethyl]-methyl-carbamic acid tert-butyl ester

[0230]

[Formula 49]



[0231]

In 50 mL of tetrahydrofuran, 200 mg (1.51 mmol) of

1H-indole-4-ol and 527 mg (3.00 mmol) of 2-hydroxyethyl-methylcarbamic acid tert-butyl ester were dissolved, and 1.51 mL (3.00 mmol) of a diethyl azodicarboxylate 40% toluene solution and 788 mg (3.00 mmol) of triphenyl-phosphine were added thereto and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was concentrated, and then distributed between ethyl acetate and a saturated ammonium chloride aqueous solution. The organic layer was washed with a saturated sodium chloride solution, dried and concentrated, and the obtained residue was purified by a silica gel column (50g, n-hexane:ethyl acetate=2:1) to obtain 433 mg (99%) of [2-(1H-indol-4-yloxy)ethyl]-methyl-carbamic acid tert-butyl ester as a viscous oily substance.

[0232]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.48(9H,s), 3.06(3H,s), 3.70(2H,br.s), 4.52(2H,br.s), 6.50(1H,d,J=7.3 Hz), 6.63(1H,t,J=2.1 Hz), 7.02-7.15(3H,m), 8.19(1H,br.s)

ESI (LC-MS positive mode) m/z 291 (M+H)

[0233]

Step B

[2-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester (Table 1, Compound No. 20)

[0234]

[Formula 50]

[0235]

The title compound can be synthesized from [2-(1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by using the same techniques as in Example 1.

[0236]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.38(9H,d,J=11.3 Hz), 2.94(2H,d,J=6.8 Hz), 3.63(2H,t,J=5.4 Hz), 4.22(2H,br), 6.63(1H,d,J=3.0 Hz), 6.65(1H,br), 7.10 (2H,d,J=4.5 Hz), 7.48(3H,m), 7.63-7.70(4H,m), 8.13(1H,d,J=2.7 Hz), 9.12(1H,br), 9.30(1H,br)

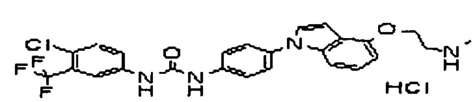
ESI (LC-MS positive mode) m/z 603 (M+H)

[Example 21]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-methylamino-ethoxy)-indol-1-yl]phenyl}urea hydrochloride (Table 1, Compound No. 21)

[0237]

[Formula 51]



[0238]

In 5 ml of a 4N hydrogen chloride ethyl acetate solution, 200 mg (0.33 mmol) of [2-(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indol-4-yloxy)-ethyl]-methylcarbamic acid tert-butyl ester was dissolved

and the solution was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and then the obtained residue was triturated with ethyl acetate to obtain 110 mg (66%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-methyl-amino-ethoxy)-indol-1-yl]phenyl}urea hydrochloride.

[0239]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 2.71(3H,t,J=5.4 Hz), 3.42(2H,br.s), 4.39(2H,t,J=4.8 Hz), 6.68(1H,dd,J=6.8, 1.6 Hz), 6.85(1H,d,J=3.5 Hz), 7.08-7.17(2H,m), 7.48(2H,d,J=8.7 Hz), 7.53(1H,d,J=2.9 Hz), 7.65-7.70(4H,m), 8.14(1H,d,J=2.1 Hz), 9.48(1H,s), 9.74(1H,s)

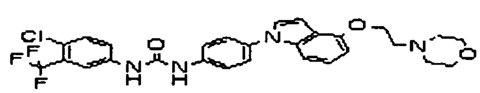
ESI (LC-MS positive mode) m/z 503 (M+H)

[Example 22]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-morpholin-4-yl-ethoxy]indol-1-yl]phenyl}urea (Table 1, Compound No. 22)

[0240]

[Formula 52]



[0241]

The title compound can be synthesized from 1H-indole-4-ol, 2-morpholin-4-ylethanol, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Example 20.

[0242]

^{1}H-NMR (270 MHz, $CDCl_3$) δ(ppm): 2.68(4H,t,J=4.6 Hz),

2.94(2H,t,J=5.4 Hz), 3.76(4H,t,J=4.6 Hz), 4.32(2H,t,J=5.4 Hz), 6.58(1H,t,J=4.1 Hz), 6.70(1H,s), 6.77(1H,d,J=3.2 Hz), 6.81(1H,s), 7.12(2H,d,J=4.9 Hz), 7.19(1H,d,J=3.2 Hz), 7.43-7.51(5H,m), 7.63(1H,d,J=7.3 Hz), 7.73 (1H,d,J=2.4 Hz)

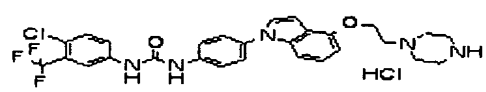
ESI (LC-MS positive mode)m/z 559(M+H)

[Example 23]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-piperazin-1-yl-ethoxy]-indol-1-yl]phenyl}urea (Table 1, Compound No. 23)

[0243]

[Formula 53]



[0244]

The title compound can be synthesized from 1H-indole-4-ol, 4-(2-hydroxyethyl)piperazine-1-carboxylic acid tert-butyl ester, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Example 20 and Example 21.

[0245]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.10-3.80(10H,br.s), 4.53(2H,br.s), 6.68(1H,dd,J=6.8, 1.6 Hz), 6.80(1H,d,J=3.5 Hz), 7.08-7.18(2H,m), 7.48(2H,d,J=8.7 Hz), 7.53(1H,d,J=2.9 Hz), 7.65-7.70(4H,m), 8.14(1H,d,J=2.1 Hz), 9.42(1H,s), 9.66(1H,s)

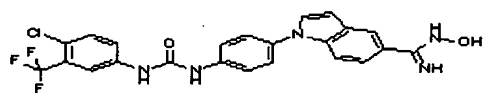
ESI (LC-MS positive mode) m/z 558 (M+H)

[Example 24]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-N-hydroxy-1H-indole-5-carboxamidine (Table 1, Compound No. 24)

[0246]

[Formula 54]



[0247]

In 10 mL of ethanol, 91 mg (0.20 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cycanoindol-1-yl)phenyl]urea was dissolved, and 109 μL (o.79 mmol) of triethylamine and 55 mg (0.79 mmol) of hydroxylamine hydrochloride were added thereto, and the mixture solution was heated and refluxed for 5 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the obtained residue was recrystallized from methanol to obtain 51.6 mg (53%) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine (Table 1, Compound No. 24).

[0248]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 5.78(2H,br.s), 6.72(1H,d,J=3.3 Hz), 7.45-7.68(10H,m), 7.96(1H,s), 8.14(1H,d,J=2.0 Hz), 9.08(1H,s), 9.23(1H,s), 9.47(1H,s)

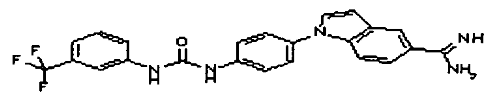
ESI (LC-MS positive mode) m/z 488.5 (M+H)

[Example 25]

1-{4-[3-(3-(Trifluoromethyl)phenyl)ureido]phenyl}-1H-indole-5-carboxamidine (Table 1, Compound No. 25)

[0249]

[Formula 55]



[0250]

In 10 mL of methanol, 12 mg (0.025 mmol) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine was dissolved and the solution was subjected to hydrogenation catalytic reduction on 10 % palladium carbon in a hydrogen atmosphere at room temperature for 14 hours. After removal of the palladium carbon by a membrane filter, the filtrate was concentrated under reduced pressure, and the obtained product was triturated from diethyl ether to obtain 3 mg (25%) of 1-{4-[3-(3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-indole-5-carboxamidine (Table 1, Compound No. 25).

[0251]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.90-6.98(1H,m), 7.25-7.35(2H,m), 7.45-7.85(8H,m), 8.03(1H,d,J=4.9 Hz), 8.24(1H,s), 8.49(1H,s), 8.62(0.5H,s), 8.79(0.5H,s), 8.93(0.5H,s), 9.09(0.5H,s), 9.24(0.5H,s), 9.34(0.5H,s), 9.38(0.5H), 9.47(0.5H,s)

ESI (LC-MS positive mode) m/z 438 (M+H)

[Example 26]

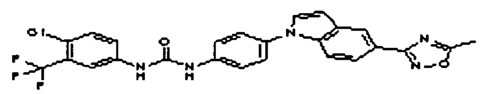
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[5-(5-

methyl-[1,2,4]oxadiazol-3-yl)indol-1-yl]phenyl}urea

(Table 1, Compound No. 26)

[0252]

[Formula 56]



[0253]

In 0.2 mL of pyridine, 10.5 mg (0.022 mmol) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine was dissolved, and 10 mg (0.098 mmol) of acetic anhydride was added thereto, and the mixture solution was stirred at 80°C for 14 hours. The reaction solution was concentrated under reduced pressure, and then the obtained residue was purified by Megabond Elute Silica Gel (a product of Varian, 1g, methylene chloride:methanol=20:1) to obtain 4.1 mg (37%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-{4-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)indol-1-yl]phenyl}urea (Table 1, Compound No. 26).

[0254]

^{1}H-NMR (270 MHz, CD_3ODO) δ (ppm): 2.68(3H,s), 6.78(1H,d,J=3.3 Hz), 7.45-7.53(3H,m), 7.55-7.68(5H,m), 7.87(1H,dd,J=1.7, 8.6 Hz), 7.96(1H,d,J=2.3 Hz), 8.37(1H,d,J=1.3 Hz),

ESI (LC-MS positive mode) m/z 512.0 (M+H)

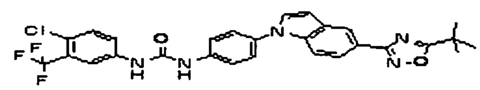
[Example 27]

1-{4-[5-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)indol-1-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)urea

(Table 1, Compound No. 27)

[0255]

[Formula 57]



[0256]

The title compound can be synthesized from 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine and pivalic anhydride by using the same techniques as in Example 26.

[0257]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.44(9H,s), 6.63(1H,d,J=3.3 Hz), 7.13(1H,d,J=3.0 Hz), 7.20-7.40(7H,m), 7.50(1H,dd,J=2.3, 8.5 Hz), 7.58(1H,d,J=2.3 Hz), 7.62(1H,br.s), 7.78(1H,dd,J=1.7, 8.6 hz), 8.36(1H,d,J=1.3 Hz)

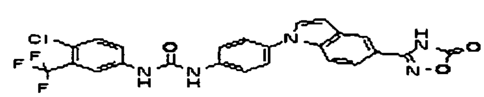
ESI (LC-MS positive mode) m/z 554 (M+H)

[Example 28]

1-(4-Chloro-3-fluoromethyl)phenyl)-3-{4-[5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)indol-1-yl]-phenyl}urea (Table 1, Compound No. 28)

[0258]

[Formula 58]



[0259]

The title compound can be synthesized from 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-

hydroxy-1H-indole-5-carboxamidine and ethyl chloroformate by using the same techniques as in Example 26.

[0260]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.84(1H,d,J=3.2 Hz), 7.55(1H,d,J=8.4 Hz), 7.65-7.71(6H,m), 7.77(1H,d,J=3.2 Hz), 8.14-8.16 (2H,m), 9.13(1H,s), 9.26(1H,s)

ESI (LC-MS positive mode) m/z 514.0 (M+H)

[Example 29]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}urea

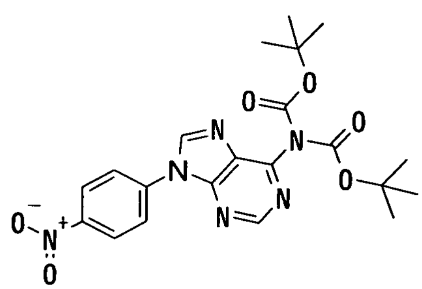
(Table 1, Compound No. 29)

Step A

Preparation of 6-di-tert-butoxycarbonylamino-9-(4-nitrophenyl)-9H-purine

[0261]

[Formula 59]



[0262]

In 100 mL of dimethyl sulfoxide, 4.05 g (30.0 mmol) of adenine was dissolved, and 3.5 g (31.0 mmol) of potassium tert-butoxide and 5.0 g (35.0 mmol) of 4-fluoronitrobenzene were added thereto and the mixture solution was stirred at 80°C for three hours. The solution was diluted with 200 mL of water, and the formed

precipitate was collected by filtration, washed with water, and vacuum dried. The obtained product (6.66 g) dissolved in 20 mL of dimethyl sulfoxide, and 17.1 g (78.0 mmol) and 0.35 g (2.86 mmol) of 4-dimethylaminopyridine were added thereto, and the mixture solution was stirred at room temperature for six hours. The reaction solution was distributed between ethyl acetate and a saturated sodium chloride solution, and the organic layer was further washed with a saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue was separated by a silica gel column (Wako Gel C-200: 300 g, n-hexane:ethyl acetate=2:1) to obtain 7.86 g (57%) of 6-di-tert-butoxycarbonylamino-9-(4-nitrophenyl)-9H-purine as a white solid.

[0263]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50(9H,s), 1.56(9H,s), 8.09(2H,d,J=8.4 Hz), 8.45-8.52(3H,m), 8.98(1H,s)

ESI (LC-MS positive mode) m/z 457 (M+H)

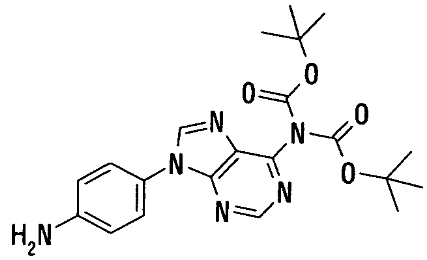
[0264]

Step B

Preparation of 9-(4-aminophenyl)6-di-tert-butoxycarbonylamino-9H-purine

[0265]

[Formula 60]



[0266]

The title compound can be synthesized from 6-di-tert-butoxycarbonylamino-9-(4-nitrophenyl)-9H-prine by using the same techniques as in Step B of Example 1.

ESI (LC-MS positive mode)m/z 427(M+H)

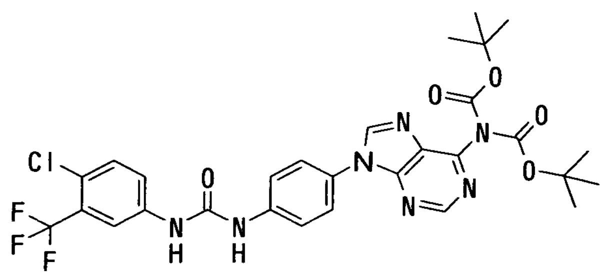
[0267]

Step C

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}urea (Table 1, Compound No. 29)

[0268]

[Formula 61]



[0269]

The title compound can be synthesized from 9-(4-aminophenyl)-6-di-tert-butoxycarbonylamino-9H-purine and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Step C of Example 1.

[0270]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.41(18H,s), 7.65-7.86(6H,m), 8.14(1H,d,J=2.0 Hz), 8.91(1H,s), 9.02(1H,s), 9.18(1H,s), 9.28(1H,s)

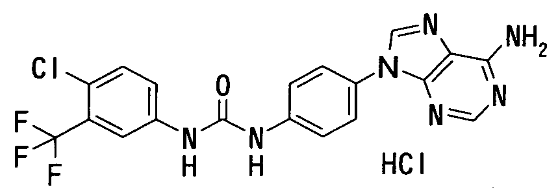
ESI (LC-MS positive mode) m/z 648 (M+H)

[Example 30]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 30)

[0271]

[Formula 62]



[0272]

In a 3 mL of a 4N hydrogen chloride ethyl acetate solution, 32 mg (0.049 mmol) of 1-(4-chloro-3-(trifluoromethyl)-3-{4-[6-(di-tert-butoxycarbonyl amino)purin-9-yl]phenyl}urea was dissolved, and the solution was stirred at room temperature for three hours. After concentrating the reaction solution, the residue was tritulated with diethyl ether to obtain 22 mg (quantitative) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethylphenyl)urea hydrochloride (Table 1, Compound No. 30) as a white solid.

[0273]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(2H,s), 7.71(4H,s), 8.14(1H,s), 8.51(1H,s), 8.82(1H,s),

9.57(1H,s), 9.76(1H,s)

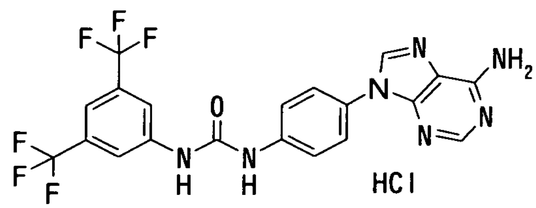
ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 31]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(3,5-bis-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 31)

[0274]

[Formula 63]



[0275]

The title compound can be synthesized from 3,5-bis-(trifluoromethyl)phenyl isocyanate by the same methods as in Examples 29 and 30.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(2H,s), 7.70-7.77(3H,m), 8.14(2H,s), 8.54(1H,s), 8.88(1H,s), 9.57(1H,s), 9.88(1H,s)

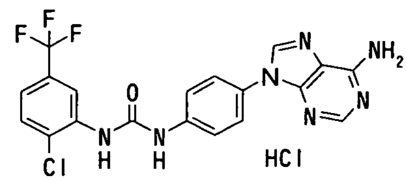
ESI (LC-MS positive mode) m/z 482 (M+H)

[Example 32]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(2-chloro-5-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 32

[0276]

[Formula 64]



[0277]

The title compound can be synthesized from 2-chloro-5-(trifluoromethyl)phenyl isocyanate by the same methods as in Examples 29 and 30.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.29(1H,dd,J=2.0, 8.3 Hz), 7.70-7.77(5H,m), 8.48(1H,s), 8.64(1H,d,J=2.0 Hz), 8.80(1H,s), 8.86(1H,s), 10.19(1H,s)

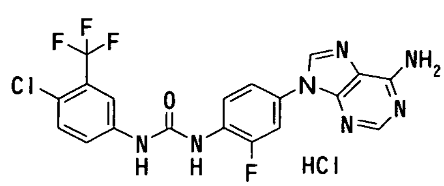
ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 33]

1-[4-(6-Aminopurin-9-yl)-2-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 33)

[0278]

[Formula 65]



[0279]

The title compound can be synthesized from adenine, 2,4-difluoronitrobenzene and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by the same method as in Examples 29 and 30.

[0280]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.43-7.60(4H,m),

7.96(1H,d,J=2.0 Hz), 8.14(1H,d,J=5.6, 8.0 Hz), 8.43(2H,s), 8.62(1H,s), 9.95(1H,s)

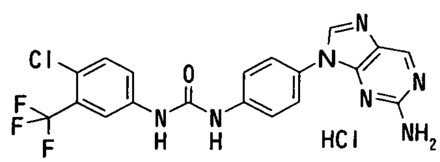
ESI (LC-MS positive mode) m/z 466 (M+H)

[Example 34]

1-[4-(2-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 34)

[0281]

[Formula 66]



[0282]

The title compound can be synthesized from 2-aminopurine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same methods as in Examples 29 and 30.

[0283]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65-7.73(6H,m), 8.12(1H,d,J=2.0 Hz), 8.73(1H,s), 8.96(1H,s), 9.46(1H,s), 9.65(1H,s)

ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 35]

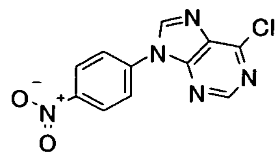
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-methoxy-ethylamino)purin-9-yl]phenyl}urea hydrochloride (Table 1, Compound No. 35)

Step A

Preparation of 6-chloro-9-(4-nitrophenyl)-9H-purine

[0284]

[Formula 67]



[0285]

The title compound can be synthesized from 2-chloropurine and 4-fluoronitrobenzene by the same method as in Step A of Example 1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 8.27-8.33(2H,m), 8.51-8.56(2H,m), 8.95(1H,s), 9.32(1H,s)

ESI (LC-MS positive mode) m/z 276 (M+H)

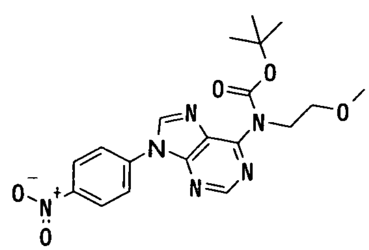
[0286]

Step B

Preparation of (2-methoxyethyl)-[9-(4-nitrophenyl)-9H-purin-6-yl]carbamic acid tert-butyl ester

[0287]

[Formula 68]



[0288]

In 1 mL of isopropanol, 100 mg (0.36 mmol) of 6-chloro-9-(4-nitrophenyl)-9H-purine was dissolved, and 400 mg (5.3 mmol) of 2-methoxyethylamine was added thereto, and the mixtue solution was stirred at 80°C for four hours.

The reaction solution was concentrated under reduced pressure and then distributed between ethyl acetate and a saturated sodium chloride solution. The organic layer was further washed with a saturated sodium chloride solution, dried and then concentrated under reduced pressure. The obtained residue was dissolved in 1 mL of dimethylformamide, and 4 mg (0.525 mmol) of dibutyl dicarbonate and the 114 mg (0.035 mmol) of 4-dimethylaminopyridine were added thereto, and the mixture solution was stirred at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by Megabond Elute Silica Gel (5 g, n-hexane:ethyl acetate=1:1) to obtain 118 mg (72%) of (2-methoxyethyl)-[9-(4-nitrophenyl)-9H-purin-6-yl]-carbamic acid tert-butyl ester.

[0289]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.50(9H,s), 3.25(3H,s), 3.65(2H,t,J=5.7 Hz), 3.70(2H,br.s), 7.96(1H,s), 8.27-8.33(2H,m), 8.49-8.52(2H,m), 8.85(1H,s)

ESI (LC-MS positive mode) m/z 315 (M+H)

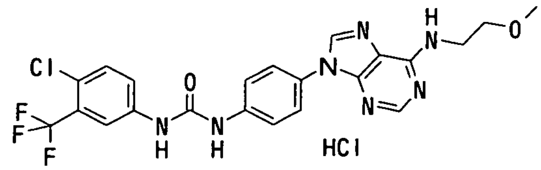
[0290]

Step C

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(2-methoxy-ethylamino)purin-9-yl]-phenyl}urea hydrochloride (Table 1, Compound No. 35)

[0291]

[Formula 69]



[0292]

The title compound can be synthesized from (2-methoxyethyl)-[9-(4-nitrophenyl)-9H-purin-6-yl]carbamic acid tert-butyl ester and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by the methods of Steps B and C of Example 1 and Example 30.

[0293]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.29(3H,s), 3.59(2H,br.s), 3.73(2H,br.s), 7.60-7.80(7H,m), 8.13(1H,s), 8.40(1H,br.s), 8.72(1H,br.s), 9.50(1H,br.s), 9.70(1H,br.s)

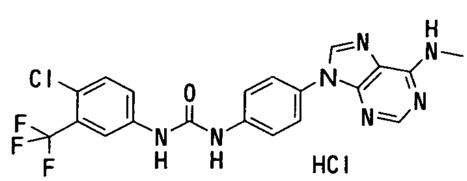
ESI (LC-MS positive mode) m/z 506 (M+H)

[Example 36]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(6-(methylamino)purin-9-yl)phenyl]urea hydrochloride (Table 1, Compound No. 36)

[0294]

[Formula 70]



[0295]

The title compound can be synthesized from 6-chloropurine, methylamine, 4-fluoronitrobenzene and

4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same method as in Example 35.

[0296]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.54(3H,s), 7.60-7.80(7H,m), 8.13(1H,s), 8.46(1H,s), 8.73(1H,s), 9.52(1H,s), 9.72(1H,s)

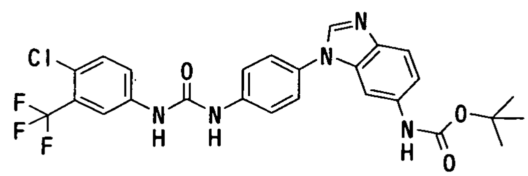
ESI (LC-MS positive mode) m/z 462 (M+H)

[Example 37]

3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-3H-benzimidazol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 37)

[0297]

[Formula 71]



[0298]

The title compound can be synthesized from 6-amino-1H-benzimidazole, di-tert-butyl dicarbonate, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same method as in Example 16.

[0299]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50 (9H,s), 6.87(1H,s), 6.98(1H,dd,J=1.9, 8.6 Hz), 7.34-7.50(7H,m), 7.65(1H,s), 7.70(1H,d,J=8.9Hz), 7.85(1H,s), 7.97(1H,s)

ESI (LC-MS positive mode) m/z 546 (M+H)

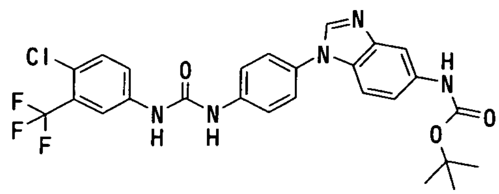
[Example 38]

(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido-

phenyl}-1H-benzimidazol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 38)

[0300]

[Formula 72]



[0301]

The title compound can be synthesized from 6-amino-1H-benzimidazole, di-tert-butyl dicarbonate, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same method as in Example 16.

[0302]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.50(9H,s), 7.37-7.50(2H,m), 7.55-7.70(6H,m), 7.88(1H,s), 8.12(1H,d,J=2.0 Hz), 8.42(1H,s), 9.11(1H,s), 9.25(1H,s), 9.34(1H,s)

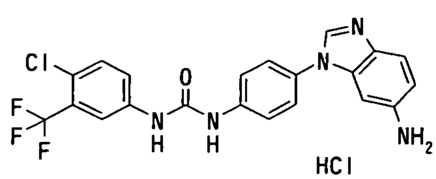
ESI (LC-MS positive mode) m/z 546 (M+H)

[Example 39]

1-[4-(6-Aminobenzimidazol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 39)

[0303]

[Formula 73]



[0304]

The title compound can be synthesized from (3-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)carbamic acid tert-butyl ester by the same method as in Example 17.

[0305]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.79(2H,br.s), 7.20-7.27(2H,m), 7.60-7.82(7H,m), 8.14(1H,s), 9.39(1H,s), 9.96(1H,s), 10.11(1H,s)

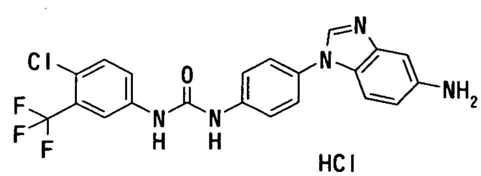
ESI (LC-MS positive mode) m/z 446 (M+H)

[Example 40]

1-[4-(6-Aminobenzimidazol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 40)

[0306]

[Formula 74]



[0307]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid tert-butyl ester by the same method as in Example 17.

[0308]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.23(1H,d,J=9.5 Hz), 7.52(1H,s), 7.63-7.77(7H,m), 8.13(1H,s), 9.32(1H,s), 9.85(1H,s), 10.00(1H,s)

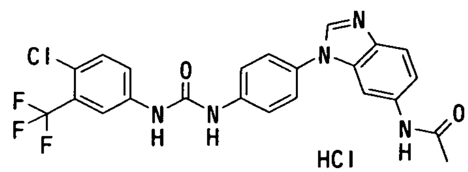
ESI (LC-MS positive mode) m/z 446 (M+H)

[Example 41]

N-(3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-3H-benzimidazol-5-yl)acetamide (Table 1, Compound No. 41)

[0309]

[Formula 75]



[0310]

In a mixed solution of 2 mL of methylene chloride and 1 mL of pyridine, 40 mg (0.083 mmol) of 1-[4-(6-amino-benzimidazol-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)urea hydrochloride was dissolved, and 0.016 mL (0.16 mmol) of acetic anhydride was added thereto and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and the residue was distributed between ethyl acetate and a saturated ammonium chloride aqueous solution. The organic layer was washed with a saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue was triturated with n-hexane:ethyl acetate=1:2 to obtain 28 mg (70%) of N-(3-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)acetamide (Table 1, Compound No. 41) as a white solid.

[0311]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.04(3H,s), 7.32 (1H,dd,J=1.6, 8.8 Hz), 7.55(2H,d,J=8.9 Hz), 7.62-

7.70(5H,m), 8.11(2H,dd,J=2.0, 8.9 Hz), 9.39(1H,s), 9.15(1H,s), 9.28(1H,s), 10.05(1H,s)

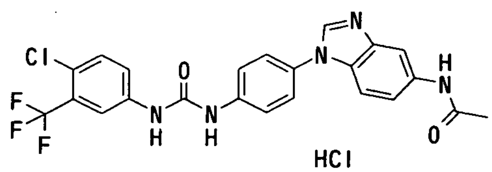
ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 42]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-benzimidazol-5-yl)acetamide (Table 1, Compound No. 42)

[0312]

[Formula 76]



[0313]

The title compound can be synthesized from 1-[4-[5-aminobenzimidazol-1-yl]phenyl]-3-(4-chloro-3-(trifluoro-methyl)phenyl)urea hydrochloride and acetic anhydride by the same method as in Example 41.

[0314]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.07(3H,s), 7.41-7.55(2H,m), 7.62-7.70(6H,m), 8.12(2H,dd,J=2.0, 5.9 Hz), 8.45(1H,s), 9.13(1H,s), 9.26(1H,s), 9.98(1H,s)

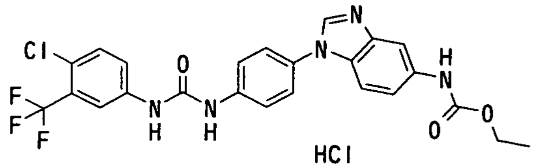
ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 43]

(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid ethyl ester (Table 1, Compound No. 43)

[0315]

[Formula 77]



[0316]

The title compound can be synthesized from 1-[4-[5-aminobenzimidazol-1-yl]phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride and ethyl chloroformate by the same method as in Example 41.

[0317]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.27(3H,t,J=7.0 Hz), 4.15(2H,q,J=7.0 Hz), 7.41-7.70(7H,m), 7.91(1H,s), 8.11-8.13(2H,m), 8.45(1H,d,J=3.5 Hz), 9.13(1H,s), 9.25(1H,s), 9.63(0.5H,s), 9.99(0.5H,s)

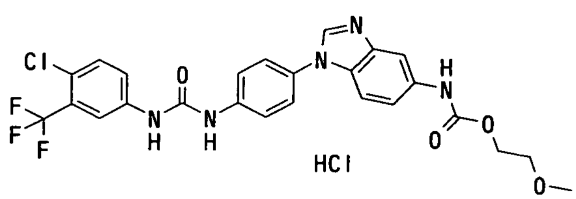
ESI (LC-MS positive mode) m/z 518 (M+H)

[Example 44]

(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid 2-methoxyethyl ester (Table 1, Compound No. 44)

[0318]

[Formula 78]



[0319]

The title compound can be synthesized from 1-[4-(5-aminobenzimdazol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride and methoxyethyl

chloroformate by the same method as in Example 41.

[0320]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.27(3H,s), 3.57(2H,m), 4.22(2H,m), 7.41-7.70(7H,m), 7.92(1H,s), 8.11-8.13(2H,m), 8.45(1H,d,J=3.5 Hz), 9.13(1H,s), 9.26(1H,s), 9.76(0.5H,s), 9.99(0.5H,s)

ESI (LC-MS positive mode) m/z 548 (M+H)

[Example 45]

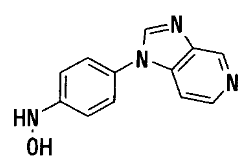
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 45)

Step A

Preparation of N-(4-imidazo[4,5-c]pyridin-1-yl-phenyl)hydroxylamine

[0321]

[Formula 79]



[0322]

In 3 mL of dioxane, 40 mg (0.167 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine obtained in Step A of Example 1 was dissolved, and 40 mg of zinc powder and 1 mL of a saturated ammonium chloride aqueous solution were added thereto and the mixture solution was vigorously stirred at room temperature for one hour. The reaction solution was distributed between ethyl acetate and water. The organic layer was washed with a sodium chloride

solution, dried and then concentrated under reduced pressure to obtain a crude product of N-(4-imidazo[4,5-c]pyridine-1-ylphenyl)-hydroxylamine. The product was used in the next reaction without further purification.

[0323]

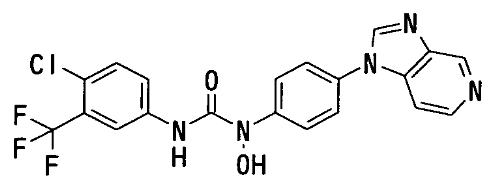
ESI (LC-MS positive mode) m/z 227 (M+H)

Step B

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxy-3-(4-imidazo[4,5-c]pyridin-1 ylphenyl)urea (Table 1, Compound No. 45)

[0324]

[Formula 80]



[0325]

In 5 mL of methylene chloride, 37 mg of N-(4-imidazo[4,5-c]pyridin-1-yl-phenyl)hydroxylamine obtained in Step A was dissolved, and 41 mg (1.84 mmol) of 4-chloro-3-(trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for three hours. The reaction solution was concentrated, and then the residue was distributed between ethyl acetate and a saturated ammonium chloride aqueous solution. The organic layer was washed with a saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue was triturated with n-hexane:ethyl acetate=1:1 to obtain

12 mg (16%) of 1-(4-chloro-3-(trifluoromethyl) phenyl)-3-hydroxy-3-(4-imidazo-[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 45) as a white solid.

[0326]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.62-7.76(7H,m), 8.14-8.43(2H,m), 8.55(1H,m), 8.98(1H,m), 10.00(1H,s), 11.10(1H,s)

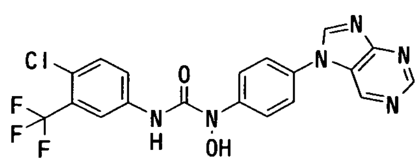
ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 46]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-(4-purin-7-ylphenyl)urea (Table 1, Compound No. 46)

[0327]

[Formula 81]



[0328]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0329]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(1H,d,J=10.9 Hz), 7.82(4H,dd,J=25.3, 13.0 Hz), 8.04(1H,dd,J=9.2, 3.7 Hz), 8.33(1H,d,J=2.3 Hz), 9.08(2H,d,J=6.8 Hz), 9.24(1H,s), 10.0(1H,s), 11.06(1H,s)

ESI (LC-MS positive mode) m/z 449 (M+H)

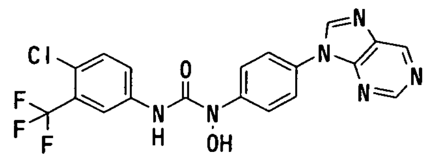
[Example 47]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-

(4-purin-9-ylphenyl)urea (Table 1, Compound No. 47)

[0330]

[Formula 82]



[0331]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0332]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.66(1H,d,J=8.9 Hz), 7.88(4H,dd,J=20.3, 12.8 Hz), 8.05(1H,dd,J=8.9, 2.3 Hz), 8.33(1H,d,J=2.3 Hz), 9.02(2H,d,J=1.3 Hz), 9.92(1H,s), 9.96(1H,s), 11.0(1H,s)

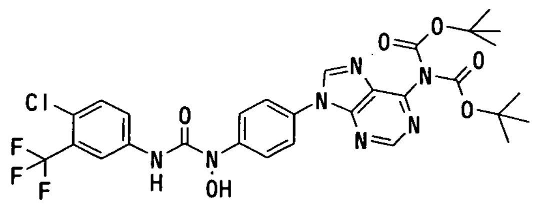
ESI (LC-MS positive mode) m/z 449 (M+H)

[Example 48]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-3-hydroxyurea (Table 1, Compound No. 48)

[0333]

[Formula 83]



[0334]

The title compound can be synthesized from 6-di-tert-

butoxycarbonylamino-9-(4-nitrophenyl)-9H-purine and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0335]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50(9H,s), 7.44(1H,d,J=8.6 Hz), 7.62(2H,d,J=7.0 Hz), 7.77(1H,dd,J=8.9, 3.0 Hz), 7.86(2H,d,J=7.2 Hz), 7.79(1H,d,J=2.7 Hz), 8.2(1H,s), 8.48(1H,d,J=4.3 Hz), 8.83(1H,s), 9.43(1H,br.s)

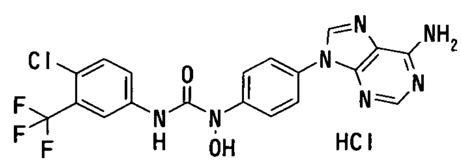
ESI (LC-MS positive mode)m/z 664(M+H)

[Example 49]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea hydrochloride (Table 1, Compound No. 49)

[0336]

[Formula 84]



[0337]

The title compound can be synthesized from 1-(4-chloro-3-(trifluoromethyl)phenyl-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-3-hydroxyurea by using the same techniques as in Example 30.

[0338]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(1H,d,J=8.9 Hz), 7.80(4H,dd,J=15.9, 9.3 Hz), 8.04(1H,dd,J=8.9, 2.3 Hz), 8.34(1H,d,J=3.6 Hz), 8.43(1H,s), 8.79(1H,s), 9.98(1H,s),

11.05(1H,s)

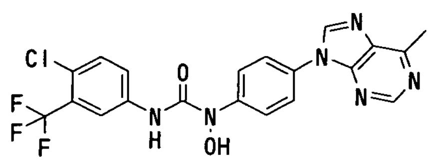
ESI (LC-MS positive mode) m/z 464 (M+H)

[Example 50]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-1-[4-(6-methylpurin-9-yl)phenyl]urea (Table 1, Compound No. 50)

[0339]

[Formula 85]



[0340]

The title compound can be synthesized from 6-methylpurine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0341]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.80(3H,s), 7.65(1H,d,J=8.9 Hz), 7.87(4H,dd,J=8.5, 7.6 Hz), 8.05(1H,dd,J=8.6, 2.6 Hz), 8.34(1H,d,J=2.6 Hz), 8.85(1H,s), 8.98(1H,s), 9.98(1H,s), 11.01(1H,s)

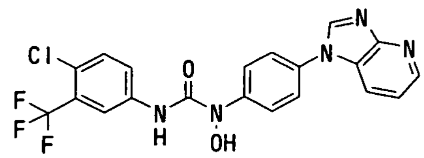
ESI (LC-MS positive mode) m/z 463 (M+H)

[Example 51]

3-(4-Chloro-3-trifluoromethyl)phenyl)-1-hydroxy-1-(4-imidazo[4,5-b]pyridin-1-ylphenyl)urea (Table 1, Compound No. 51)

[0342]

[Formula 86]



[0343]

The title compound can be synthesized from imidazo-[4,5-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0344]

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.40(1H,dd,J=3.2 4.8 Hz), 7.66(1H,d,J=9.2 Hz), 7.83(2H,d,J=8.8 Hz, 7.93(2H,d,J=8.8 Hz), 8.06(1H,d,J=7.6 Hz), 8.22(1H,d,J=8.0 Hz), 8.35(1H,d,J=2.4 Hz), 8.45(1H,d,J=4.8 Hz), 8.90(1H, s), 9.98(1H,s), 10.99(1H,s)

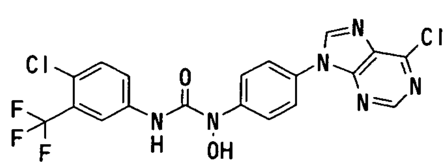
ESI (LC-MS positive mode)m/z 448 (M+H)

[Example 52]

1-[4-(6-Chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea (Table 1, Compound No. 52)

[0345]

[Formula 87]



[0346]

The title compound can be synthesized from 6-chloropurine, 4-fluoronitrobenzene and 4-chloro-3-

(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0347]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(1H,d,J=8.5 Hz), 7.88(4H,d), 8.04(1H,dd,J=8.5, 2.3 Hz), 8.32(1H,d,J=2.5 Hz), 8.85(1H,s), 9.12(1H, s), 10.01(1H,s), 11.03(1H,s)

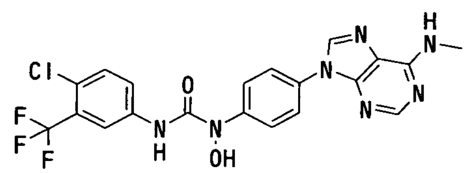
ESI (LC-MS positive mode) m/z 483 (M+H)

[Example 53]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-1-[4-(6-(methylamino)pruin-9-yl)phenyl]urea (Table 1, Compound No. 53)

[0348]

[Formula 88]



[0349]

In 2 mL of a 40% methylamine methanol solution, 30 mg (0.062 mmol) of 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea was dissolved and the solution stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure, and then the residue was purified by Megabond Elute Silica Gel (1 g, ethyl acetate:methanol= 10:1) to obtain 3.21 mg (11%) of 3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-1-[4-(6-(methylamino)pruin-9-yl)-phenyl]urea (Table 1, Compound No. 53)

[0350]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.15(3H,br.s), 7.67(1H,d,J=8.1 Hz), 7.82(4H,m), 8.06(1H,dd,J=8.2, 2.5 Hz), 8.28(1H,s), 8.35(1H,d,J=2.6 Hz), 8.56(1H,s), 9.96(1H,s), 10.98(1H,s)

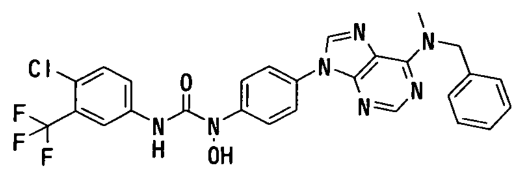
ESI (LC-MS positive mode) m/z 478 (M+H)

[Example 54]

1-{4-[6-(Benzyl-methylamino)purin-9-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea (Table 1, Compound No. 54)

[0351]

[Formula 89]



[0352]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)-1-hdroxyurea and benzylmethylamine by using the same techniques as in Example 53.

[0353]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.27(3H,s), 7.26-7.32(5H,m), 7.38(1H,d,J=13.4 Hz), 7.42(2H,d,J=12.8 Hz), 7.54(1H,dd,J=13.4, 2.6 Hz), 7.65(2H,d,J=12.3 Hz), 7.80(1H,d,J=2.7 Hz), 7.89(1H, s), 8.15(1H,s), 8.39(1H,s)

ESI (LC-MS positive mode) m/z 568 (M+H)

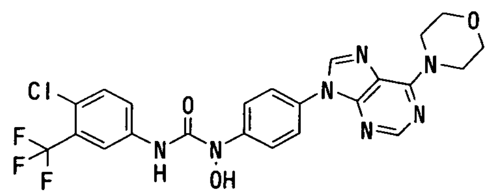
[Example 55]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-3-[4-(6-(morpholin-4-yl)purin-9-yl)phenyl]urea (Table 1,

Compound No. 55)

[0354]

[Formula 90]



[0355]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-1-hydroxyurea and morpholine by using the same techniques as in Example 53.

[0356]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.77(4H,t,J=4.8 Hz), 4.27(4H,br), 7.65(1H,d,J=8.9 Hz), 7.82(4H,s), 8.03(1H,dd,J=8.9, 2.6 Hz), 8.32(2H,d,J=2.5 Hz), 8.61(1H,s), 9.97(1H,s), 10.98(1H,s)

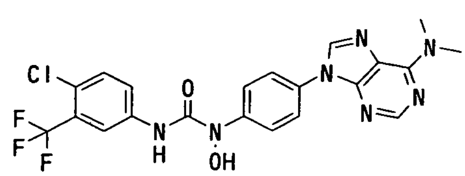
ESI (LC-MS positive mode) m/z 534 (M+H)

[Example 56]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-[4-(6-dimethylamino-purin-9-yl)phenyl]-1-hydroxyurea (Table 1, Compound No. 56)

[0357]

[Formula 91]



[0358]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)-1-hydroxyurea and dimethylamine by using the same techniques as in Example 53.

[0359]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.51(6H,br), 7.67(1H,d,J=8.1 Hz), 7.82(4H,m), 8.06(1H,dd,J=8.2, 2.5 Hz), 8.28(1H,s), 8.35(1H,d,J=2.6 Hz), 8.56(1H,s), 9.96(1H,s), 10.98(1H,s)

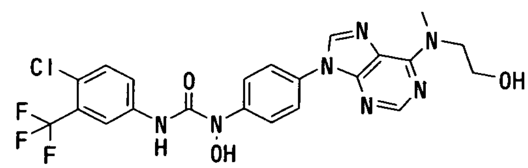
ESI (LC-MS positive mode) m/z 492 (M+H)

[Example 57]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-(4-{6-[(2-hydroxyethyl)-methylamine]purin-9-yl}-phenyl)urea (Table 1, Compound No. 57)

[0360]

[Formula 92]



[0361]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)-1-hydroxyurea and 2-methylaminoethanol by using the same techniques as in Example 53.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.71(2H,br), 4.80(1H,br), 7.66(1H,d,J=8.9 Hz), 7.82(4H,m), 8.05(1H,dd,J=8.9, 2.6 Hz), 8.27(1H,s), 8.33(1H,d,J=2.3 Hz), 8.56(1H,s), 9.97(1H,s), 10.99(1H,s)

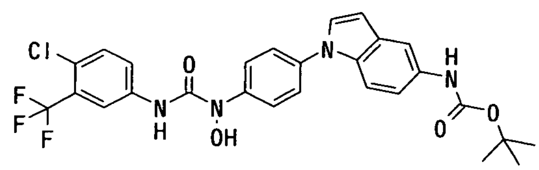
ESI (LC-MS positive mode) m/z 522 (M+H)

[Example 58]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 58)

[0362]

[Formula 93]



[0363]

The title compound can be synthesized from (1H-indol-5-yl)-carbamic acid tert-butyl ester, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 53.

[0364]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.56(9H,s), 6.57(2H,d,J=2.7 Hz), 6.88-7.01(2H,br), 7.15-7.70(9H,m), 7.83(1H,d,J=2.6 Hz), 8.18(1H,s), 8.37(1H,s)

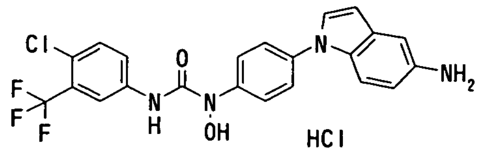
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 59]

1-[4-(5-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)1--hydroxyurea hydrochloride (Table 1, Compound No. 59)

[0365]

[Formula 94]



[0366]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]-phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 17.

[0367]

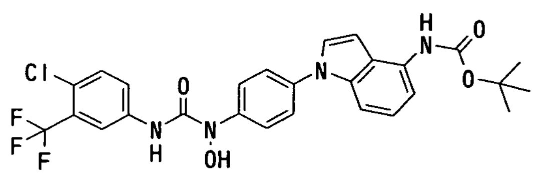
ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 60]

(1-{4-[3-(4-Chloro-3-(trifluormethyl)phenyl)-1-hydroxyureido]phenyl}-1H-indol-4-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 60)

[0368]

[Formula 95]



[0369]

The title compound can be synthesized from 4-aminoindole, di-tert-butyl dicarbonate, 4-fluoronitro-benzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0370]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.55(9H,s), 6.52(1H,br), 6.71(1H,s), 7.04-7.56(6H,m), 7.65(1H,m), 7.88(1H,s), 8.17(1H, s), 8.30(1H,br)

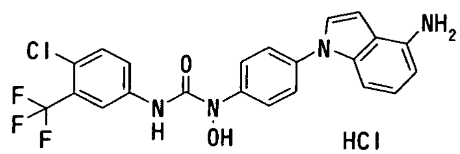
ESI (LC-MS positive mode) m/z 505 (M+H)

[Example 61]

1-[4-(4-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea hydrochloride (Table 1, Compound No. 61)

[0371]

[Formula 96]



[0372]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]-phenyl}-1H-indol-4-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 17.

[0373]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.85(1H,d,J=3.2 Hz), 7.10(1H,d,J=7.6 Hz), 7.21(1H,t,J=8.3 Hz), 7.48(1H,d,J=8.5 Hz), 7.56(2H,d,J=8.5 Hz), 7.65(1H,d,J=8.2 Hz), 7.75(1H,d,J=3.3 Hz), 7.80(2H,d,J=8.5 Hz), 8.14(1H,dd,J=9.0, 2.8 Hz), 9.95(1H,s), 11.02(1H,br)

ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 62]

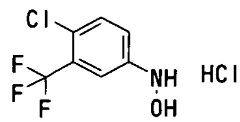
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-1-hydroxyurea (Table 1, Compound No. 62)

Step A

Preparation of N-(4-chloro-3-(trifluoromethyl)-phenyl)hydroxylamine hydrochloride

[0374]

[Formula 97]



[0375]

In 21 mL of ethanol, 4.51 g (20 mmol) of 2-chloro-5-nitrobenzotrifluoride was dissolved, and a solution obtained by dissolving 3.8 g of zinc powder and 420 mg of ammonium chloride in 5 mL of water was added thereto, and the mixture solution was stirred at 70°C for one hour. The reaction solution after removal of insolubles by filtration was concentrated, and the residue was distributed between water and ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried, and then concentrated under reduced pressure, and to the obtained residue, 30 mL of a 4N hydrogen chloride ethyl acetate solution was added, and the formed white precipitate was collected by filtration, washed with ethyl acetate and vacuum dried to obtain 3.08 g (63%) of N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydro-chloride.

[0376]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.10(1H,dd,J=2.6, 8.5 Hz), 7.29(1H,d,J=2.6 Hz), 7.48(1H,d,J=8.5 Hz) 7.55(3H,br.s)

ESI (LC-MS positive mode) m/z 249 (M+H)

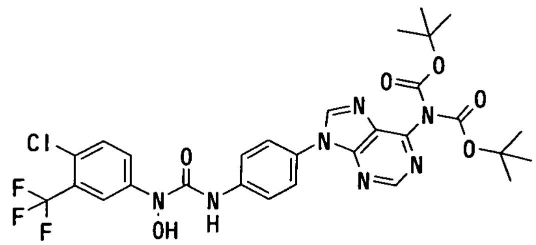
[0377]

Step B

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-1-hydroxyurea (Table 1, Compound No. 62)

[0378]

[Formula 98]



[0379]

In 6 mL of methylene chloride, 100 mg (2.35 mmol) of 9-(4-aminophenyl)-6-di-tert-butoxycarbonylamino-9H-purine prepared in Step B of Example 29 was dissolved, and 28 mg (0.94 mmol) of triphosgene was added thereto at one time. Successively, 0.042 mL (2.42 mmol) of Hunig's base was added thereto and the resulting solution was stirred at room temperature for five minutes. To the formed slurry, 64 mg (2.59 mmol) of N-(4-chloro-3-(trifluoromethyl)-phenyl)hydroxylamine hydrochloride dissolved in 0.123 mL of Hunig's base and 4 mL of methylene chloride was added dropwise and the resulting solution was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate (100 mL) and water

(100 mL), and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the residue was purified by Megabond Elute Silica Gel (5 g, n-hexane:ethyl acetate=1:1) to obtain 57 mg (37%) of 1-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonyl-amino)purin-9-yl]phenyl}-1-hydroxyurea (Table 1, Compound No. 62) as a white solid.

[0380]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50(18H,s), 6.80(1H,m), 7.39(1H,d,J=9.0 Hz), 7.48(1H,d,J=9.2 Hz), 7.62(4H,dd,J=26.1, 8.9 Hz), 7.82(1H,s), 8.03(1Hm), 8.15(1H,s), 8.22(1H,s), 8.28(1H,s), 8.74(1H,br), 8.88(1H,s)

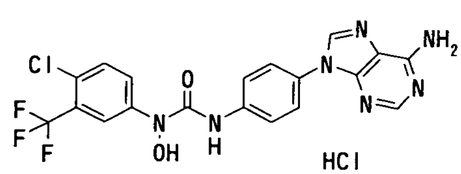
ESI (LC-MS positive mode) m/z 664 (M+H)

[Example 63]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxyurea hydrochloride (Table 1, Compound No. 63)

[0381]

[Formula 99]



[0382]

The title compound can be synthesized from (1-(4-chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxy-carbonylamino)purin-9-yl]phenyl}-1-hydroxyurea by using the

same techniques as in Example 30.

[0383]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.38(1H,d,J=8.6 Hz), 7.66-7.78(4H,m), 7.95(3H,d,J=6.9 Hz), 8.20(1H,d,J=2.7 Hz), 8.55(1H,d,J=2.6 Hz), 8.83(1H,d,J=4.3 Hz), 9.86(1H,s)

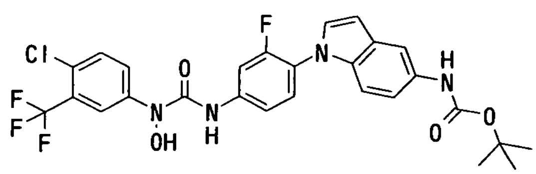
ESI (LC-MS positive mode) m/z 464 (M+H)

[Example 64]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 64)

[0384]

[Formula 100]



[0385]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride and [1-(4-amino-2-fluorophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester by using the same techniques as in Example 62.

[0386]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.52(9H,s), 6.60(1H,d,J=3.6 Hz), 7.08(1H,d,J=8.9 Hz), 7.22(1H,d,J=8.9 Hz), 7.44(1H,d,J=1.0 Hz), 7.55(1H,t,J=8.9 Hz), 7.68-7.78(3H,m), 7.85-7.95(2H,m) 8.18(1H,d,J=2.3 Hz), 9.19(1H,s), 10.00(1H,s),

11.19(1H,s)

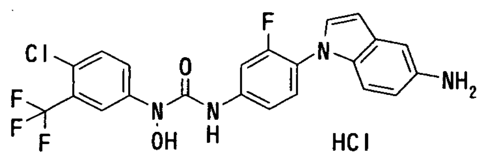
ESI (LC-MS positive mode) m/z 523.03 (M+H-t-Bu)

[Example 65]

3-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-1-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea (Table 1, Compound No. 65)

[0387]

[Formula 101]



[0388]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 30.

[0389]

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 6.81(1H,d,J=2.8 Hz), 7.16 (1H,d,J=2.4, 8.8 Hz), 7.32(1H,d,J=9.6 Hz), 7.55(1H,t,J=8.8 Hz), 7.67(2H,d,J=2.0 Hz), 7.73-7.76(2H,m), 7.93(2H,d,J=11.2 Hz), 8.19(1H,d,J=2.4 Hz), 10.04(1H,s), 10.09(2Hbr.s), 11.27(1H,s)

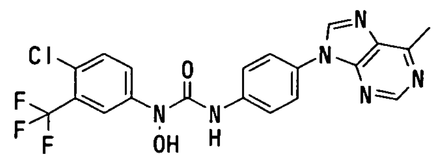
ESI (LC-MS positive mode) m/z 463.2 (M+H)

[Example 66]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-1-[4-(6-methylpurin-9-yl)phenyl]urea (Table 1, Compound No. 66)

[0390]

[Formula 102]



[0391]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 6-methylpurine and 4-fluoronitrobenzene by using the same techniques as in Example 62.

[0392]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.79(3H,s), 7.70(1H,d,J=8.9 Hz), 7.81-7.98(5H,m), 8.19(1H,d,J=2.7 Hz), 8.83(1H,s), 8.90(1H,s), 9.86(1H,s), 11.12(1H,s)

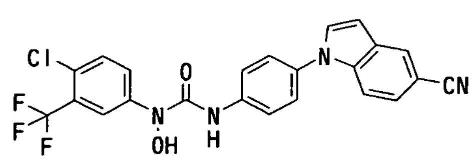
ESI (LC-MS positive mode) m/z 463 (M+H)

[Example 67]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cyanoindol-1-yl)phenyl]-1-hydroxyurea (Table 1, Compound No. 67)

[0393]

[Formula 103]



[0394]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 5-cyanoindole and 4-fluoronitrobenzene by using the same techniques as in Example 62.

[0395]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.84(1H,d,J=3.3 Hz), 7.52-7.59(3H,m), 7.64(1H,d,J=8.9 Hz), 7.73(1H,d,J=8.9 Hz), 7.86(1H,d,J=3.3 Hz), 7.89-7.96(3H,m), 8.20(2H,m), 9.96(1H,s), 11.11(1H,s)

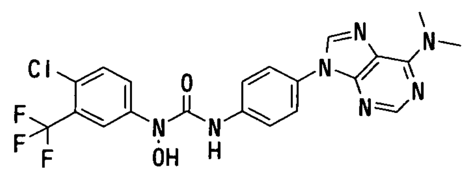
ESI (LC-MS positive mode) m/z 471.1 (M+H)

[Example 68]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(6-dimethylaminopurin-9-yl)phenyl]-3-hydroxyurea (Table 1, Compound No. 68)

[0396]

[Formula 104]



[0397]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride and [9-(4-aminophenyl)-9H-purin-6-yl]-dimethylamine by using the same techniques as in Example 62.

[0398]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 7.70(1H,d,J=9.2 Hz), 7.80(4H,dd,J=30.0, 8.9 Hz), 7.91(1H,dd,J=8.9, 2.6 Hz), 8.19(1H,d,J=2.7 Hz), 8.27(1H,s), 8.52(1H,s), 9.83(1H,s), 11.12(1H,s)

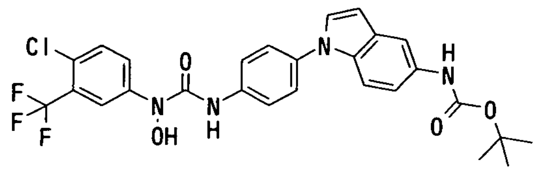
ESI (LC-MS positive mode) m/z 492 (M+H)

[Example 69]

(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 69)

[0399]

[Formula 105]



[0400]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, (1H-indol-5-yl)-carbamic acid tert-butyl ester and 4-fluoronitrobenzene by using the same techniques as in Example 62.

[0401]

^{1}H-NMR (270 MHz, $CDCl_3$) δ(ppm): 1.53(9H,s), 6.59(1H,d,J=3.3 Hz), 7.11(1H,dd,J=8.9, 2.3 Hz), 7.30(1H,d,J=3.3 Hz), 7.35-7.48(4H,m), 7.64(2H,d,J=6.6 Hz), 7.70(1H, br), 7.87(1H,dd, J=8.9, 2.7 Hz), 8.08(1H,d,J=2.7 Hz), 8.55(1H,s)

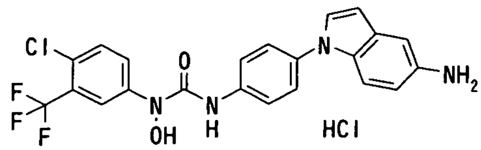
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 70]

(1-[4-(5-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride (Table 1, Compound No. 70)

[0402]

[Formula 106]



[0403]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 30.

[0404]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.78(1H,d,J=3.3 Hz), 7.18(1H,dd,J=8.9, 2.4 Hz), 7.53(2H,d,J=8.9 Hz), 7.55-7.80(3H,m), 7.88(2H,d,J=9.8 Hz), 8.20(1H,d,J=2.7 Hz), 9.80(1H,s), 10.11(1H, br), 11.16(1H,s)

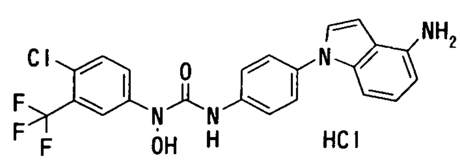
ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 71]

1-[4-(4-Aminoindol-1yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride (Table 1, Compound No. 71)

[0405]

[Formula 107]



[0406]

The titled compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 4-aminoindol, di-tert-butyl dicarbonate and 4-fluoronitrobenzene by using the same techniques as in

Example 70.

[0407]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.84(1H,d,J=3.3 Hz), 7.02(1H,d,J=7.5 Hz), 7.19(1H,t,J=7.6 Hz), 7.42(1H,d,J=7.9 Hz), 7.51(2H,d,J=8.9 Hz), 7.77-7.84(2H,m), 7.89(2H,d,J=8.9 Hz), 8.20(1H,d,J=2.6 Hz), 9.80(1H,s), 11.12(1H,s)

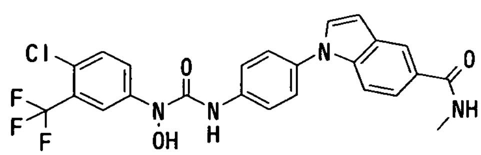
ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 72]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indole-5-carboxylic acid methylamide (Table 1, Compound No. 72)

[0408]

[Formula 108]



[0409]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 1-(4-aminophenyl)-1H-indole-5-carboxylic acid methylamide by using the same techniques as in Example 62.

[0410]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.82(3H,d,J=4.3 Hz), 6.80(1H,d,J=3.3 Hz), 7.53-7.58(3H,m), 7.68-7.74(3H,m), 7.85-7.93(3H,m), 8.20(2H,m), 8.37(1H,q,J=4.3 Hz), 9.83(1H,s), 11.12(1H,s)

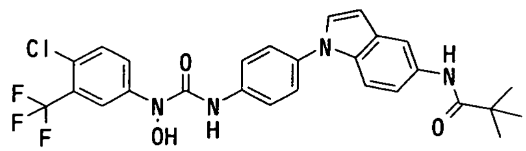
ESI (LC-MS positive mode) m/z 503.5 (M+H)

[Example 73]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-2,2-dimethylpropionamide (Table 1, Compound No. 73)

[0411]

[Formula 109]



[0412]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and pivalic anhydride by using the same techniques as in Example 41.

[0413]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.23(9H,s), 6.62(1H,d,J=3.3 Hz), 7.34(1H,d,J=8.9 Hz), 7.46(1H,d,J=8.9 Hz), 7.50(2H,d,J=8.9 Hz), 7.56(1H,d,J=3.3 Hz), 7.72(1H,d,J=8.9 Hz), 7.87(2H,d,J=8.9 Hz), 7.90-7.96(2H,m), 8.20(1H,d,J=2.3 Hz), 9.12(1H,s), 9.78(1H,s), 11.09 (1H,s)

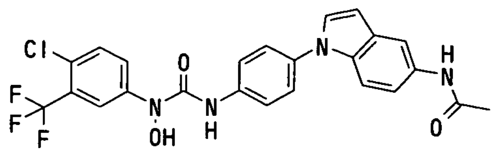
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 74]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)acetamide (Table 1, Compound No. 74)

[0414]

[Formula 110]



[0415]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and acetic anhydride by using the same techniques as in Example 41.

[0416]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 2.04(3H,s), 6.62(1H,d,J=4.3 Hz), 7.27(1H,dd,J=9.3, 2.0 Hz), 7.35-7.65(4H,m), 7.70(1H,d,J=8.9 Hz), 7.83(2H,d,J=9.0 Hz), 7.94(1H,dd,J=9.2, 2.7 Hz), 7.97(1H,s), 8.20(1H,d,J=2.7 Hz), 9.78(1H,s), 9.86(1H,s), 11.09(1H,s)

ESI (LC-MS positive mode) m/z 503 (M+H)

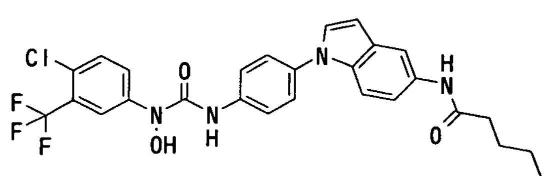
[Example 75]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)pentanamide

(Table 1, Compound No. 75)

[0417]

[Formula 111]



[0418]

The title compound can be synthesized from 1-[4-(5-

aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-valeroyl chloride by using the same techniques as in Example 41.

[0419]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.90(3H,q,J=5.1 Hz), 1.31(2H,m), 1.61(2H,m), 2.31(1H,t,J=6.5 Hz), 2.76(1H,t,J=5.5 Hz), 6.62(1H,d,J=3.3 Hz), 7.29(1H,dd,J=8.9, 2.0 Hz), 7.46(1H,d,J=8.9 Hz), 7.55(2H,d,J=8.9 Hz), 7.58(1H,d,J=3.3 Hz), 7.70(2H,d,J=8.9 Hz), 7.74(1H,d,J=2.1 Hz), 7.78(1H,d,J=8.9 Hz), 7.94(1H,d,J=2.6 Hz), 8.00(1H,d,J=2.6 Hz), 9.65(1H,s), 9.77(1H,s)

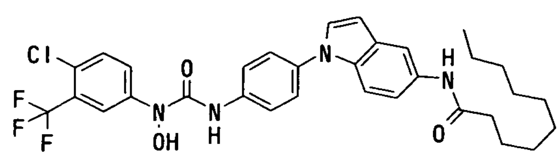
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 76]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)decanamide (Table 1, Compound No. 76)

[0420]

[Formula 112]



[0421]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-decanoyl chloride by using the same techniques as in Example 41.

[0422]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 0.89(3H,t,J=6.3 Hz), 1.27(14H,br), 2.32(2H,d,J=8.0 Hz), 6.61(1H,d,J=3.3 Hz), 7.06-7.31(5H,m), 7.35-7.50(3H,m), 7.71(1H,d,J=2.3 Hz), 7.75(1H,s), 7.78(1H,d,J=2.7 Hz), 9.81(1H,br)

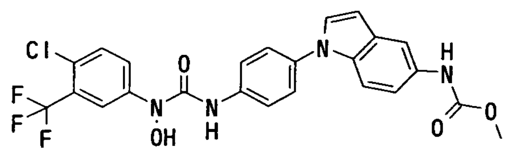
ESI (LC-MS positive mode) m/z 615 (M+H)

[Example 77]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid methyl ester (Table 1, Compound No. 77)

[0423]

[Formula 113]



[0424]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and methyl chloroformate by using the same techniques as in Example 41.

[0425]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 3.71(3H,s), 6.60(1H,d,J=3.0 Hz), 6.75(1H,s), 7.04(1H,d,J=8.9 Hz), 7.15-7.30(5H,m), 7.36(1H,d,J=8.9 Hz), 7.51(1H,s), 7.68-7.72(2H,m), 7.93(1H,d,J=2.6 Hz), 8.93(1H,br)

ESI (LC-MS positive mode) m/z 519 (M+H)

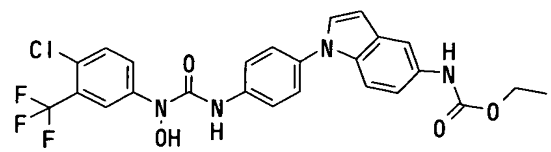
[Example 78]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-

hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid ethyl ester (Table 1, Compound No. 78)

[0426]

[Formula 114]



[0427]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and ethyl chloroformate by using the same techniques as in Example 41.

[0428]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.23(3H,t,J=7.1 Hz), 4.14(2H,q,J=7.2 Hz), 6.62(1H,d,J=2.6 Hz), 6.63(1H,s), 7.09(1H,dd,J=8.9, 2.0 Hz), 7.25-7.45(6H,m), 7.53(1H,d,J=2.0 Hz), 7.75(1H,dd,J=8.2, 2.3 Hz), 7.95(1H,d,J=2.6 Hz)

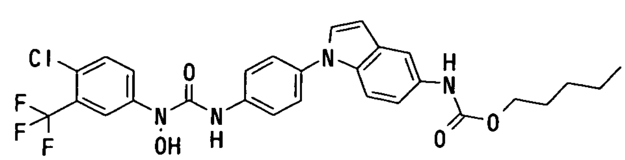
ESI (LC-MS positive mode) m/z 533 (M+H)

[Example 79]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid pentyl ester (Table 1, Compound No. 79)

[0429]

[Formula 115]



[0430]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-pentyl chloroformate by using the same techniques as in Example 41.

[0431]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 0.91(3H,t,J=6.6 Hz), 1.32(4H,m), 1.62(2H,m), 4.03(2H,t,J=6.6 Hz), 6.61(1H,d,J=2.6 Hz), 6.70(1H,s), 7.07(1H,dd,J=8.5, 2.0 Hz), 7.16-7.35(6H,m), 7.37(1H,d,J=8.9 Hz), 7.51(1H,d,J=2.0 Hz), 7.72(1H,br), 7.75(1H,s), 7.95(1H,s)

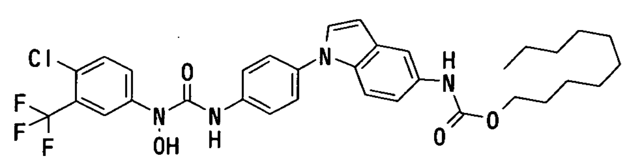
ESI (LC-MS positive mode) m/z 557 (M+H)

[Example 80]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid decyl ester (Table 1, Compound No. 80)

[0432]

[Formula 116]



[0433]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-decyl chloroformate by using the same techniques as in Example 41.

[0434]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 0.89(3H,m), 1.30(14H,br),

1.61(2H,m), 4.03(2H,t,J=7.0 Hz), 6.60(1H,d,J=3.3 Hz), 6.68(1H,s), 6.76(1H,d,J=8.9 Hz), 7.07(1H,dd,J=9.0, 2.0 Hz), 7.17-7.36(6H,m), 7.38(1H,d,J=8.8 Hz), 7.52(1H,d,J=2.0 Hz), 7.66-7.75(2H,m), 7.95(1H,d,J=2.7 Hz), 8.92(1H,br)

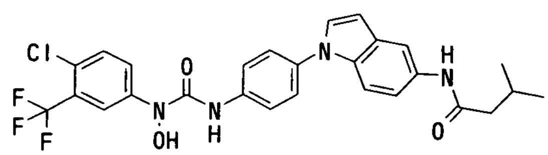
ESI (LC-MS positive mode) m/z 645 (M+H)

[Example 81]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3-methylbutyl-amide (Table 1, Compound No. 81)

[0435]

[Formula 117]



[0436]

The titled compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and isovaleroyl chloride by using the same techniques as in Example 41.

[0437]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.95(6H,d,J=6.3 Hz), 2.12(1H,m), 2.21(2H,m), 6.62(1H,d,J=2.3 Hz), 7.29(1H,d,J=8.9 Hz), 7.45-7.95(7H,m), 8.00(1H,d,J=2.0 Hz), 8.19(1H,d,J=2.7 Hz), 9.75(2H,d,J=5.9 Hz), 11.08(1H,s),

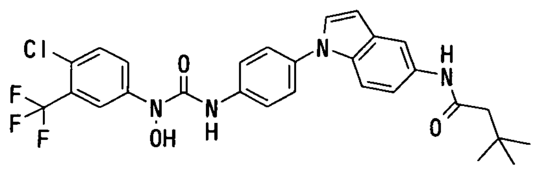
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 82]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3,3-dimethyl-butylamide (Table 1, Compound No. 82)

[0438]

[Formula 118]



[0439]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and tert-butylacetyl chloride by using the same techniques as in Example 41.

[0440]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.03(9H,s), 2.20(2H,s), 6.62(1H,d,J=3.2 Hz), 7.27(1H,d,J=10.8 Hz), 7.45(1H,d,J=8.9 Hz), 7.51(2H,d,J=8.9 Hz), 7.59(1H,d,J=8.9 Hz), 7.72(1H,d,J=9.2 Hz), 7.85(2H,d,J=8.9 Hz), 7.93(1H,d,J=11.3 Hz), 8.00(1H,s), 8.19(1H,d,J=2.4 Hz), 9.69(1H,s), 9.78(1H,s), 11.09(1H,s),

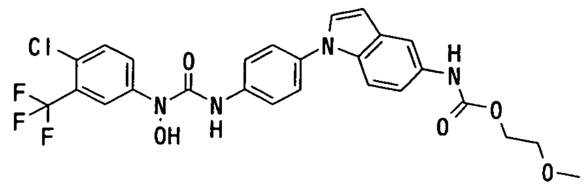
ESI (LC-MS positive mode) m/z 559 (M+H)

[Example 83]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid 2-methoxyethyl ester (Table 1, Compound No. 83)

[0441]

[Formula 119]



[0442]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and 2-methoxyethyl chloroformate by using the same techniques as in Example 41.

[0443]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.28(3H,s), 3.57(2H,t,J=5.0 Hz), 4.21(2H,t,J=5.0 Hz), 6.60(1H,d,J=3.3 Hz), 7.25(1H,d,J=8.6 Hz), 7.45(1H,d,J=8.9 Hz), 7.52(2H,d,J=8.9 Hz), 7.58(1H,d,J=3.3 Hz), 7.70(1H,d,J=8.6 Hz), 7.78(1H,br), 7.85(2H,d,J=8.9 Hz), 7.91(1H,dd,J=8.9, 2.3 Hz), 8.20(1H,d,J=2.6 Hz), 9.58(1H,br), 9.75(1H,s), 11.10(1H,s),

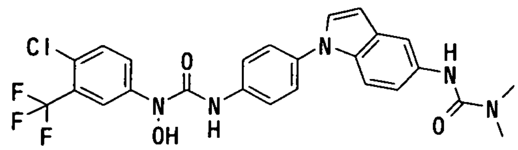
ESI (LC-MS positive mode) m/z 563 (M+H)

[Example 84]

3-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-1,1-dimethylurea (Table 1, Compound No. 84)

[0444]

[Formula 120]



[0445]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and N,N-dimethyl-carbamic acid chloride by using the same techniques as in Example 41.

[0446]

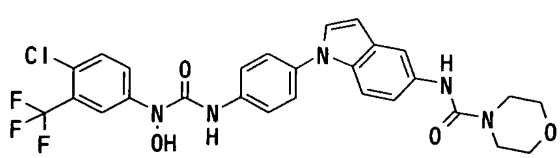
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.92(3H,s), 3.16(3H,s), 4.66(1H,br), 6.38(1H,d,J=3.0 Hz), 6.56(2H,dd,J=8.6, 2.0 Hz), 6.76(1H,d,J=2.0 Hz), 7.26(1H,d,J=8.6 Hz), 7.43(1H,d,J=3.3 Hz), 7.50(2H,d,J=8.9 Hz), 7.65(2H,d,J=8.9 Hz), 7.75(1H,d,J=8.9 Hz), 7.99(1H,d,J=2.3 Hz), 9.55(1H,s) ESI (LC-MS positive mode) m/z 532 (M+H)

[Example 85]

Morpholine-4-carboxylic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 85)

[0447]

[Formula 121]



[0448]

The title compound can be synthesized from 1-[4-(5-

aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-pheny)-3-hydroxyurea hydrochloride and 4-morpholinyl-carbamic acid chloride by using the same techniques as in Example 41.

[0449]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 3.41(4H,m), 3.63(4H,m), 6.58(1H,d,J=2.1 Hz), 7.22(1H,d,J=8.9 Hz), 7.40-7.78(6H,m), 7.85(2H,d,J=8.9 Hz), 7.96(1H,d,J=8.9 Hz), 8.19(1H,d,J=2.0 Hz), 8.45(1H,s), 9.78(1H,s), 11.08(1H,s)

ESI (LC-MS positive mode) m/z 574 (M+H)

[Example 86]

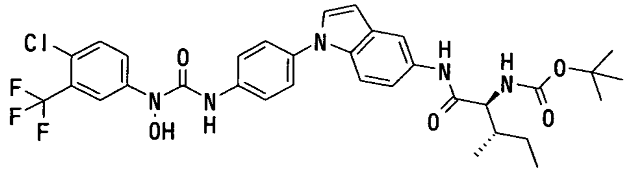
(2S,3S)-2-Amino-3-methylpentanoic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 86)

Step A

Preparation of [1-(1-{4-[3-(4-chloro-3-(trifluoro-methyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-ylcarbamoyl)-(2S,3S)-2-methylbutyl]carbamic acid tert-butyl ester

[0450]

[Formula 122]



[0451]

In a mixed solution of 0.2 mL of methanol and 2.0 mL

of methylene chloride, 80 mg (0.16 mmol) of 1-[4-(5-amino-indol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride was dissolved, and 59 mg (0.18 mmol) of tert-butyoxycarbonyl-L-isoleucine N-hydroxy-succinimide ester and 0.5 mL of pyridine were added thereto and the mixture solution was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution. The orgnic layer was dried and then concentrated under reduced pressure, and the residue was purified by Megabond Elute Silica Gel (2 g, n-hexane:ethyl acetate=1:1) to obtain 15.0 mg (14%) of [1-(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-ylcarbamoyl)-(2S,3S)-2-methylbutyl]-carbamic acid tert-butyl ester as a white solid.

[0452]

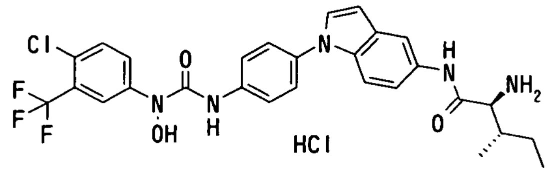
ESI (LC-MS positive mode) m/z 674 (M+H)

Step B

Preparation of (2S,3S)-2-amino-3-methylpentanoic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 86)

[0453]

[Formula 123]



[0454]

In 2 mL of a 4N hydrogen chloride ethyl acetate solution, 15.0 mg (14%) of [1-(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-ylcarbamoyl)-(2S,3S)-2-methylbutyl]carbamic acid tert-butyl ester was dissolved and the solution was stirred under cooling with ice for one hour. The reaction solution was concentrated under reduced pressure, and then the residue was triturated with diethyl ether to obtain 7.0 mg (17%) of (2S,3S)-2-amino-3-methylpentanic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-ureido]phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 86) as a white solid.

[0455]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.85-1.03(6H,m), 1.63(1H,m), 1.95(1H,br), 3.85(1H,br), 6.68(1H,d,J=3.3 Hz), 7.32-7.95(8H,m), 8.21(1H,m), 9.73(1H,d,J=6.9 Hz), 10.53(1H,br), 11.19(1H,d,J=3.3 Hz)

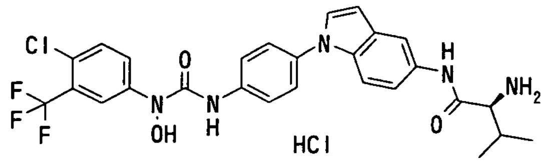
ESI (LC-MS positive mode) m/z 574 (M+H)

[Example 87]

(S)-2-Amino-N-(1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3-methylbutylamide (Table 1, Compound No. 87)

[0456]

[Formula 124]



[0457]

The title compound can be synthesized from 1-[4-(5-amonoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and tert-butoxy-carbonyl-L-valine N-hydroxysuccinimide ester by using the same techniques as in Example 86.

[0458]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.02(6H,d,J=7.0 Hz), 2.22(1H,m), 3.83(1H,br), 6.69(1H,d,J=3.3 Hz), 7.40(1H,dd,J=8.9, 2.0 Hz), 7.68(1H,d,J=8.9 Hz), 7.75-7.95(7H,m), 8.20(1H,s), 8.27(2H,br), 9.75(1H,br), 10.55(1H,br), 11.17(1H,br)

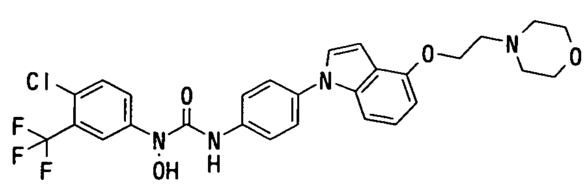
ESI (LC-MS positive mode) m/z 560 (M+H)

[Example 88]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-3-{4-[4-(2-(morpholin-4-yl)ethoxy)indol-1-yl]phenyl}-urea (Table 1, compound No. 88)

[0459]

[Formula 125]



[0460]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 1H-indole-4-ol, 2-(morpholin-4-yl)ethanol and 4-fluoronitrobenzene in the same manner as in Example 62.

[0461]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 2.55(4H,br), 2.80(2H,t,J=5.4 Hz), 3.60(4H,t,J=4.6 Hz), 4.25(2H,t,J=5.7 Hz), 6.66(2H,m), 7.11(2H,m), 7.50(3H,m), 7.70(1H,d,J=8.9 Hz), 7.86(2H,d,J=8.9 Hz), 8.20(1H,d,J=2.7 Hz), 9.79(1H,s), 11.10(1H,s)

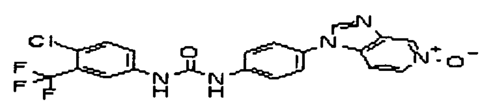
ESI (LC-MS positive mode) m/z 575 (M+H)

[Example 89]

Synthesis of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea (Table 1, Compound No. 89)

[0462]

[Formula 126]



[0463]

In 10 mL of acetic acid, 540 mg (1.25 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo[4,5-c]-pyridin-1-yl)urea prepared in Example 1 was dissolved, and 3 mL of a 30% hydrogen peroxide aqueous solution was added thereto and the mixture solution was stirred at 50°C for one day. The solvent was distilled under reduced pressure, and the residue was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm,

dichloromethane:methanol=9:1 to 4:1) to obtain 282 mg (53%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea (Table 1, Compound No. 89) as a white solid.

[0464]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 7.60-7.78(7H,m), 8.13-8.15(2H,m), 8.77(1H,s), 8.83(1H,d,J=1.3 Hz), 9.20(1H,s), 9.29(1H,s)

ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 90]

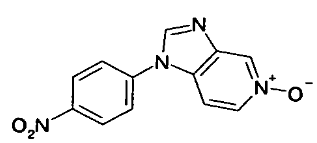
Synthesis of 1-[4-(4-chloro-imidazo[4,5-c]pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (Table 1, Compound No. 90)

<u>Step A</u>

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-pyridine 5-oxide

[0465]

[Formula 127]



[0466]

In 15 mL of acetic acid, 483 mg (2.01 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine prepared in Step A of Example 1 was dissolved, and 2 mL of a 30% hydrogen peroxide aqueous solution was added thereto and the mixture solution was stirred at 50°C for 14 hours. The solvent was distilled under reduced pressure, and the obtained residue

was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol=9:1) to obtain 298 mg (57%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine 5-oxide as a pale yellow solid.

[0467]

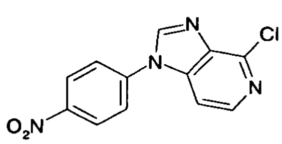
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.80 (1H,dd,J=0.6, 7.2 Hz), 8.05(2H,m), 8.20(1H,dd,J=1.7, 7.0 Hz), 8.45(2H,m), 8.87(1H,s), 8.97(1H,s)

Step B

Preparation of 4-chloro-1-(4-nitrophenyl)-1H-imidazo-[4,5-c]pyridine

[0468]

[Formula 128]



[0469]

In 5 mL of phosphorus oxychloride, 42 mg (0.164 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine 5-oxide was dissolved and the solution was stirred at 80°C for 14 hours. Excess reagent was distilled under reduced pressure, and the residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogencarbonate aqueous solution (10 mL). The combined organic layers were washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was separated by a silica gel column

(Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol=19:1) to obtain 45 mg (quantitative) of 4-chloro-1-(4-nitrophenyl)-1H-imidazo-[4,5-c]pyridine as a pale yellow solid.

[0470]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 7.48 (1H,d,J=5.6 Hz), 8.05(2H,m), 7.70-7.80(3H,m), 8.30(1H,s), 8.36(1H,d,J=5.6 Hz), 8.56(2H,m)

ESI (LC-MS positive mode) m/z 275 (M+H)

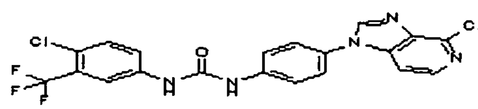
[0471]

Step C

Preparation of 1-[4-(4-chloro-imidazo[4,5-c]pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl) urea (Table 1, Compound No. 90)

[0472]

[Formula 129]



[0473]

In 50% acetic acid, 41 mg (0.150 mmol) of 4-chloro-1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine prepared in Step B was dissolved, and 42 mg (0.75 mmol) of iron powder was added thereto, and the mixture solution was stirred at 50°C for one hour. The solvent was distilled, and the obtained residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogencarbonate aqueous solution (10 mL). The combined organic layers were washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate, and

then concentrated under reduced pressure to obtain 1-(4-aminophenyl)-4-chloroimdazo-1H-[4,5-c]pyridine as a crude product. In 10 mL of dichloromethane, the crude product without further purification was dissolved, and 31 mg (0.15 mmol) of 4-chloro-3-trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for two hours. The solvent was distilled under reduced pressure, and the obtained residue was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane: methanol=19:1), and the obtained crude product was recrystallized from methanol to obtain 44 mg (63%) of 1-[4-(4-chloro-imidazo[4,5-c]pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (Table 1, Compound No. 90) as a colorless crystal.

[0474]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.60-7.67(5H,m), 7.70-7.75(2H,m), 8.14(1H,d,J=2.0 Hz), 8.23(1H,d,J=5.6 Hz), 8.79(1H,s), 9.19(1H,s), 9.29(1H,s)

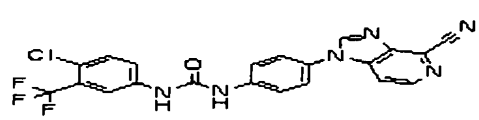
ESI (LC-MS positive mode) m/z 467 (M+H)

[Example 91]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-cyanoimidazo[4,5-c]pyridin-1-yl)phenyl]urea (Table 1, Compound No. 91)

[0475]

[Formula 130]



[0476]

In 10 mL of acetonitrile, 112 mg (0.25 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea prepared in Example 89 was dissolved, and 104 μL (0.75 mmol) of trimethylsilylcyanide and 20 μl (0.75 mmol) of 1,8-diazabicyclo[5.4.0]undecene were added thereto and the mixture solution was stirred at 80°C for six hours. The solvent was distilled under reduced pressure, and the residue was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol=9:1 to 4:1) to obtain 15 mg (15%) of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-[4-(4-cyanoimidazo[4,5-c]pyridin-1-yl)phenyl]- urea (Table 1, Compound No. 91) as a white solid.

[0477]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 7.62-7.67(4H,m), 7.70-7.75(2H,m), 7.98(1H,d,J=7.3 Hz), 8.13(1H,d,J=2.3 Hz), 8.59(1H,d,J=5.6 Hz), 8.99(1H,s), 9.19(1H,s), 9.29(1H,s)

ESI (LC-MS positive mode) m/z 457 (M+H)

[Example 92]

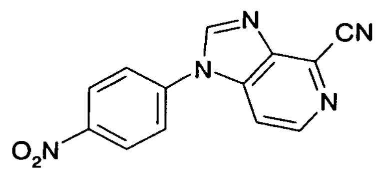
1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide (Table 1, Compound No. 92)

Step A

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-pyridine-4-carbonitrile

[0478]

[Formula 131]



[0479]

In a mixed solvent of 1 mL of dimethylformamide and 2mL of dioxane, 100 mg (0.39 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine 5-oxide prepared in Step A of Example 90 was dissolved, and 310 μL (0.78 mmol) of tri-methylsilylcyanide and 144 μL (0.78 mmol) of N,N-dimethylcarbamoyl chloride were added thereto and the mixture solution was stirred at 90°C for 14 hours. The solvent was distilled, and the residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogen-carbonate aqueous solution (10 mL). The combined organic layers was washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was triturated with ethyl acetate to obtain 78 mg (75%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carbonitrile as a pale yellow solid.

[0480]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 8.07-8.13(2H,m), 8.14-8.16(1H,m), 8.47-8.53(2H,m), 8.67(1H,d,J=5.5 Hz), 9.20(1H,s)

ESI (LC-MS positive mode) m/z 266 (M+H)

[0481]

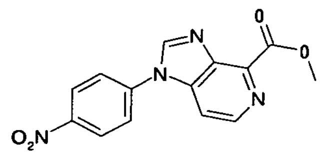
Step B

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-

pyridine-4-carboxylic acid methyl ester

[0482]

[Formula 132]



[0483]

In 10 mL of methanol, 74 mg (0.28 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carbonitrile prepared in Step A was dissolved, and 2 mL of a 4N hydrogen chloride dioxane solution was added thereto, and the mixture solution was refluxed under heating with stirring for four hours. The solvent was distilled under reduced pressure, and the residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogencarbonate aqueous solution (10 mL). The combined organic layers was washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate and then concentrated under reduced pressure. The solvent was distilled and the residue was separated by Megabond Elute Silica Gel (2 g, dichloromethane:methanol=30:1) to obtain 34 mg (41%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-5-carboxylic acid methyl ester as a white solid.

[0484]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 4.17(3H,s), 7.70-7.80(3H,m), 8.40(1H,s), 8.52-8.57(2H,m), 8.72-8.74(1H,d,J=6.3 Hz)

ESI (LC-MS positive mode) m/z 299 (M+H)

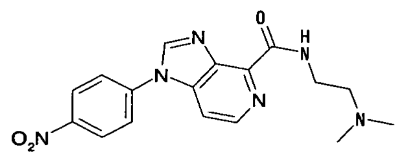
[0485]

Step C

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-pyridine-4-carboxylic acid (2-(dimethylamino)ethyl amide

[0486]

[Formula 133]



[0487]

In 5 mL of methanol, 11 mg (0.037 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methyl ester prepared in Step B was dissolved, and 100 μL of N,N-dimethylethylenediamine was added thereto and the solution was refluxed under heating with stirring for two hours. The solvent was distilled under reduced pressure, and the residue was separated by Megabond Elute Silica Gel (1 g, dichloromethane:nethanol=30:1 to 4:1) to obtain 7.3 mg (51%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide as a white solid.

[0488]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 2.30(6H,s), 2.65(2H,t,J=6.3 Hz), 3.73(2H,t,J=5.9 Hz), 7.62(1H,d, J=5.3 Hz), 7.73-7.77(2H,m), 8.39(1H,s), 8.50-8.54(2H,m), 8.64(1H,d,J=5.6 Hz), 8.90(1H,br.s)

ESI (LC-MS positive mode) m/z 355 (M+H)

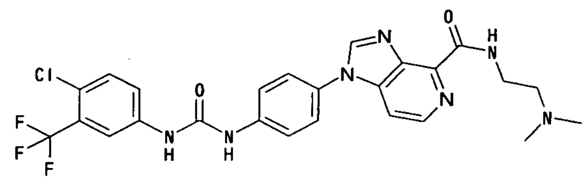
[0489]

Step D

Preparation of 1-{4-[3-(4chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide (Table 1, Compound No. 92)

[0490]

[Formula 134]



[0491]

The title compound can be synthesized from 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide and 4-chloro-3-(trifluoro-methyl)phenyl isocyanate in the same manner as in Steps B and C of Example 1.

[0492]

^{1}H-NMR (270 MHz, CD_3OD) δ(ppm): 2.39(6H,s), 2.73(2H,t,J=6.6 Hz), 3.73(2H,t,J=6.6 Hz), 7.50-7.70(4H,m), 7.73-7.77(3H,m), 8.04(1H,m), 8.54(1H,m), 8.66(1H,s)

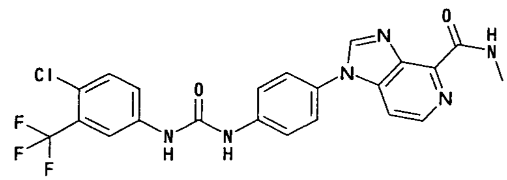
ESI (LC-MS positive mode) m/z 546 (M+H)

[Example 93]

1-{4-[3-(4-Chloro-3-(trimethylfluoro)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methylamide (Table 1, Compound No. 93)

[0493]

[Formula 135]



[0494]

The title compound can be synthesized from 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methyl ester, methylamine and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Steps C and D of Example 92.

[0495]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.39(3H,d,J=4.6 Hz), 7.62-7.80(7H,m), 8.14(1H,d,J=2.0 Hz), 8.49(1H,d,J=5.6 Hz), 8.83(1H,s), 9.02(1H,br.q,J=4.6 Hz), 9.21(1H,s), 9.30(1H,s)

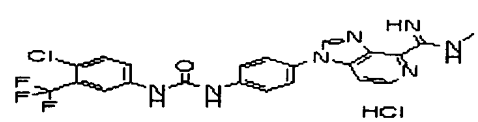
ESI (LC-MS positive mode) m/z 489 (M+H)

[Example 94]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-N-methyl-1H-imidazo[4,5-c]pyridine-4-carboxamidine hydrochloride (Table 1, Compound No. 94)

[0496]

[Formula 136]



[0497]

In 5 mL of methanol, 12 mg (0.026 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-cyanoimidazo-

[4,5-c]pyridin-1-yl)phenyl]urea prepared in Example 91 was dissolved, and one drop (a catalytic amount) of a 28% methanol solution of sodium methylate was added thereto and the solution was stirred at room temperature for six hours. The reaction solution was neutralized with one drop of acetic acid, and then 50 μL of a dimethylamine 40% methanol solution was added thereto and the mixture solution was further stirred at room temperature for 14 hours. The solvent was distilled under reduced pressure, and the residue was separated by reversed phase high-pressure liquid chromatography (C18 Column, acetonitrile:water=55:45, 0.05% trifluoroacetic acid). The fraction containing a target product was concentrated, and then trifluoroacetic acid was replaced with hydrochloric acid to obtain 4.2 mg (30%) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-methyl-1H-imidazo[4,5-c]pyridine-4-carboxamidine hydrochloride (Table 1, Compound No. 94)

[0498]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 3.20(3H,d,J=5.2 Hz), 7.63-7.8(6H,m), 8.05(1H,d,J=5.6 Hz), 8.13(1H,s), 8.68(1H,d,J=5.6 Hz), 9.16(1H,s), 9.68(1H,s), 9.73(1H,s), 9.86(1H,s), 9.89(1H,s)

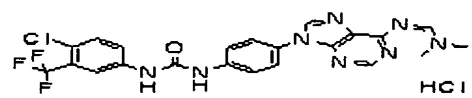
ESI (LC-MS positive mode) m/z 457 (M+H)

[Example 95]

N'-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-N,N-dimethylformamidine hydrochloride (Table 1, Compound No. 95)

[0499]

[Formula 137]



[0500]

In 10 mL of pyridine, 463 mg (0.957 mmol) of 1-[4-(6-amino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoro-methyl)phenyl)urea hydrochloride was dissolved, and 455 mg (3.83 mmol) of dimethylformamide dimethylacetal was added thereto and the mixture solution was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure, and then the residue was triturated with ethyl acetate and collected by filtration, and vacuum dried. The white solid was dissolved in 10 mL of methanol and 4N hydrochloric acid and concentrated under reduced pressure. The residue was triturated with ethyl acetate, collected by filtration, and then vacuum dried to obtain 580 mg (quantitative) of N'-(9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)-N,N-dimethylformamidine hydrochloride (Table 1, Compound No. 95) as a white solid.

[0501]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.30(3H,s), 3.45(3H,s), 4.30(1H,br.s), 7.60-7.80 (6H,q, J=7.2 Hz), 8.14(1H,m), 8.75(1H,s), 9.02(1H,s), 9.63(1H,s), 10.09(1H,s), 10.83(1H,s)

ESI (LC-MS positive mode) m/z 503 (M+H)

[Example 96]

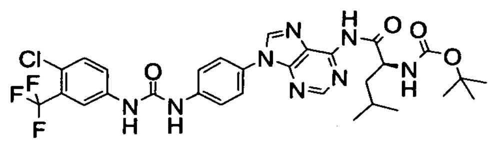
(S)-2-Amino-4-methyl-pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 96)

Step A

Preparation of [1-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-ylcarbonyl)-3-methylbutyl]carbamic acid tert-butyl ester

[0502]

[Formula 138]



[0503]

In 15 ml of tetrahydrofuran, 300 mg (0.620 mmol) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride was dissolved, and 771 mg (3.10 mmol) of tert-butoxycarbonyl-L-leucine, 1.60 g (3.10 mmol) of (benzotriazolyloxy)tripyrrolidino-phosphonium hexa-fluorophosphate (PyBOP) and 0.54 mL (3.10 mmol) of Hunig's base were added thereto and the mixture solution was stirred at room temperature for three days. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water. The organic phase was washed with a saturated sodium chloride solution, dried, and then concentated under reduced pressure. The residue was purified by Megabond Elute Silica Gel (10 g, ethyl acetate), to obtain 320 mg

(78%) of [1-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl) ureido]phenyl}-9H-purin-6-ylcarbonyl)-3-methyl-butyl]carbamic acid tert-butyl ester as a white solid.

[0504]

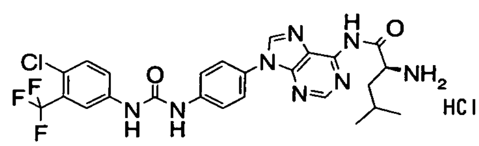
ESI (LC-MS positive mode) m/z 661 (M+H)

Step B

Preparation of (S)-2-amino-4-methyl-pentanoic acid (9-{4-[3-(4-chloro-3-(tirfluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 96)

[0505]

[Formula 139]



[0506]

In 5 mL of a 4N hydrogen chloride ethyl acetate solution, 310 mg (0.47 mmol) of [1-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-ylcarbonyl)-3-methylbutyl]carbamic acid tert-butyl ester was dissolved and the solution was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and the residue was triturated with ethyl acetate, collected by filtration, and then vacuum dried to obtain 280 mg (quantitative) of (S)-2-amino-4-methyl-pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 96).

[0507]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.90(3H,d,J=4.6 Hz), 0.96(3H,d,J=4.0 Hz), 1.60-1.65(1H,m), 1.70-1.80(2H,m), 4.40(1H, br.s), 7.65-7.83(6H,m), 8.14(1H,d,J=2.3 Hz), 8.30-8.37(3H,m), 8.75(1H,s), 8.93(1H,br.s), 9.38(1H,br.s), 9.55(1H,br.s)

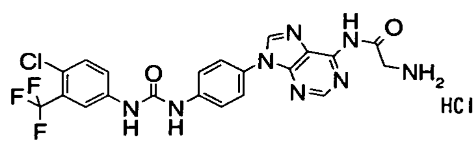
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 97]

2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)acetamide hydrochloride (Table 1, Compound No. 97)

[0508]

[Formula 140]



[0509]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-glycine by using the same method as in Example 96.

[0510]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.17(2H,m), 7.65-7.84(6H,m), 8.14(1H,d,J=2.0 Hz), 8.20-8.25(3H,m), 8.75(1H,s), 8.92(1H,s)

ESI (LC-MS positive mode) m/z 505 (M+H)

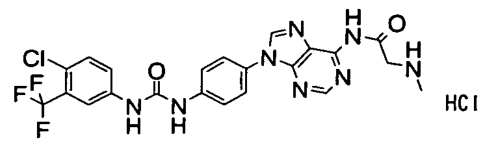
[Example 98]

N-(9-{4-[3-(4-Chloro-3-(triofluoromethyl)phenyl)-

ureido]phenyl}-9H-purin-6-yl)-2-methylaminoacetamide hydrochloride (Table 1, Compound No. 98)

[0511]

[Formula 141]



[0512]

The titled compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-sarcosine by using the same method as in Example 96.

[0513]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.30(3H,br.s), 4.87(2H, br.s), 7.65-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.87(1H,s), 8.93(1H,s), 9.48(1H,br.s), 9.53(1H,br.s), 9.67(1H,br.s)

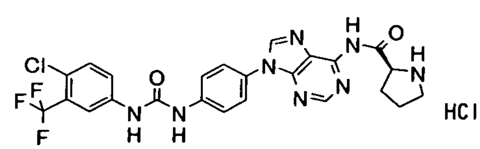
ESI (LC-MS positive mode) m/z 519 (M+H)

[Example 99]

(S)-Pyrrolidine-2-carboxylic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, compound No. 99)

[0514]

[Formula 142]



[0515]

The title compound can be synthesized from 1-[4-(6-

aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-proline by using the same method as in Example 96.

[0516]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.53-2.58(2H,m),2.62-2.68(2H,m), 3.83-3.85(1H,m), 4.34-4.36(2H,m), 7.64-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.77(1H,s), 8.93(1H,s), 8.95(1H,br.s), 9.55(1H,br.s), 9.77(1H,br.s)

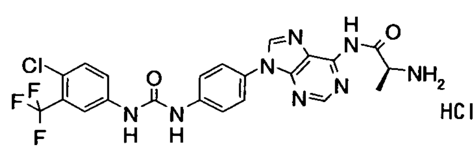
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 100]

(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl-phenyl)ureido]phenyl}-9H-purin-6-yl)propionamide hydrochloride (Table 1, Compound No. 100)

[0517]

[Formula 143]



[0518]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-alanine by using the same method as in Example 96.

[0519]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.54(3H,d,J=6.9 Hz), 4.4(1H,br.s), 7.65-7.83(6H,m), 8.14(1H,d,J=2.3 Hz), 8.30-8.37(3H,m), 8.79(1H,s), 8.93(1H,s), 8.95(1H,br.s), 9.52(1H,br.s), 9.72(1H,br.s)

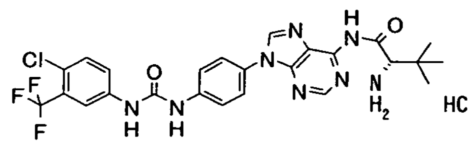
ESI (LC-MS positive mode) m/z 519 (M+H)

[Example 101]

(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3,3-dimethyl-butylamide hydrochloride (Table 1, Compound No. 101)

[0520]

[Formula 144]



[0521]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-choro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-tert-butylglycine by using the same method as in Example 96.

[0522]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.00(9H,s), 4.40(1H,br.s), 7.65-7.80(6H,m), 8.14(1H,d,J=2.0 Hz), 8.30-8.37(3H,m), 8.80(1H,s), 8.92(1H,s)

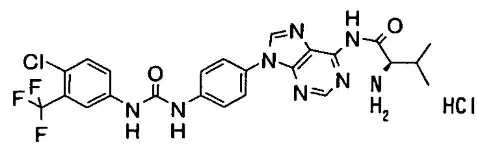
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 102]

(R)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3-methylbutyl-amide hydrochloride (Table 1, Compound No. 102)

[0523]

[Formula 145]



[0524]

The titled compound can be synthesized from 1-[4-(6-amino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-D-valine by using the same method as in Example 96.

[0525]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.07(3H,d,J=6.9 Hz), 1.13(3H,d,J=6.9 Hz), 2.30-2.35(1H,m), 4.15-4.20(1H,m), 7.66-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.30-8.40(3H,m), 8.79(1H,s), 8.92(1H,s), 9.51(1H,br.s), 9.70(1H,br.s), 11.48(1H,br.s)

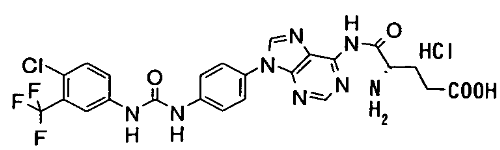
ESI (LC-MS positive mode) m/z 547 (M+H)

[Example 103]

(S)-4-Amino-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride (Table 1, Compound No. 103)

[0526]

[Formula 146]



[0527]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-

glutamic acid 5-tert-butyl ester by using the same method as in Example 96.

[0528]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.53-2.58(2H,m), 2.62-2.68(2H,m), 3.83-3.85(1H,m), 4.34-4.36(2H,m), 7.64-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.79(1H,s), 8.92(1H,s), 9.33(1H,br.s), 9.47(1H.br.s)

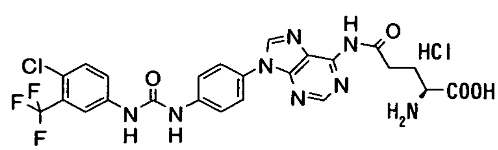
ESI (LC-MS positive mode) m/z 577 (M+H)

[Example 104]

(S)-2-Amino-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride (Table 1, Compound No. 104)

[0529]

[Formula 147]



[0530]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-clhoro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-glutamic acid 1-tert-butyl ester by using the same method as in Example 96.

[0531]

ESI (LC-MS positive mode) m/z 577 (M+H)

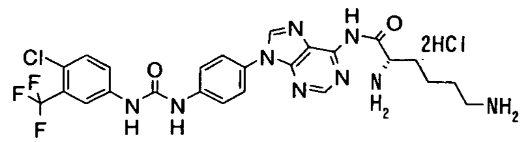
[Example 105]

(S)-2,6-Diaminohexanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-

yl)amide hydrochloride (Table 1, Compound No. 105)

[0532]

[Formula 148]



[0533]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-lysine by using the same method as in Example 96.

[0534]

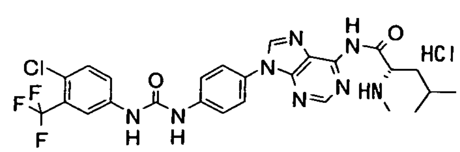
ESI (LC-MS positive mode) m/z 575 (M+H)

[Example 106]

(S)-4-Methyl-2-(methylamino)pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 106)

[0535]

[Formula 149]



[0536]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and N-methyl-tert-butoxy-carbonyl-L-leucine by using the same method as in

Example 96.

[0537]

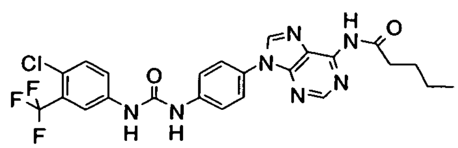
ESI (LC-MS positive mode) m/z 575 (M+H)

[Example 107]

Pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide (Table 1, Compound No. 107)

[0538]

[Formula 150]



[0539]

In 3 mL of pyridine, 30 mg (0.062 mmol) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride was dissolved, and 35 mg (0.186 mmol) of valeric anhydride and 8 mg (0.062 mmol) of 4-(N,N-dimethylamino)pyridine were added thereto, and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution, dried and concentrated. The residues was purified by Megabond Elute Silica Gel (1 g, ethyl acetate) to obtain 22.2 mg (56%) of pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide (Table 1, Compound No. 107) as a white solid.

[0540]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.93(3H,t,J=7.0 Hz), 1.37(2H,m), 1.61(2H,m), 2.59(2H,m), 7.64-7.83(6H,m), 8.14(1H,d,J=2.3 Hz), 8.68(1H,s), 8.83(1H,s), 9.16(1H,s), 9.27(1H,br.s), 10.73(1H.br.s)

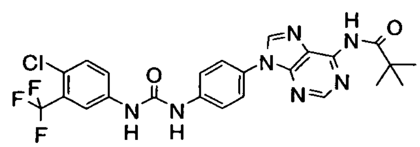
ESI (LC-MS positive mode) m/z 532 (M+H)

[Example 108]

N-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-2,2-dimethyl)-propionamide (Table 1, Compound No. 108)

[0541]

[Formula 151]



[0542]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and pivalic andhydride by using the same method as in Example 107.

[0543]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.30(9H,s), 7.60-7.82(6H,m), 8.14(1H,d,J=2.3 Hz), 8.76(1H,s), 8.81(1H,s), 9.17(1H,s), 9.28(1H,s), 10.24(1H,br.s) ESI (LC-MS positive mode) m/z 532 (M+H)

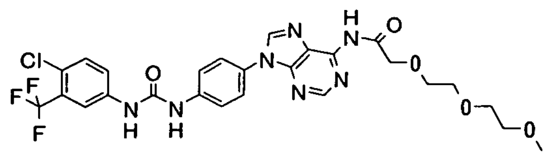
[Example 109]

N-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-2-[2-(2-methoxy)-

ethoxy]acetamide (Table 1, Compound No. 109)

[0544]

[Formula 152]



[0545]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and 2-[2-(2-methoxyethoxy)-ethoxy]acetyl chloride by using the same method as in Example 107.

[0546]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.20(2H,s), 3.41-3.45(2H,m), 3.55-3.65(4H,m), 4.69-4.75(2H,m), 4.37(3H,s), 7.64-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.73(1H,s), 8.88(1H,s), 9.25(1H,br.s), 9.39(1H,br.s), 10.45(1H,br.s)

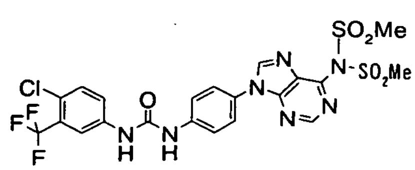
ESI (LC-MS positive mode) m/z 608 (M+H)

[Example 110]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-methanesulfonylamino)-purin-9-yl]phenyl}urea (Table 1, Compound No. 110)

[0547]

[Formula 153]



[0548]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and methanesulfonyl chloride by using the same method as in Example 107.

[0549]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.93(6H,s), 7.62-7.91(6H,m), 8.14(1H,br.s), 8.40(1H,t,J=7.9 Hz), 8.83-8.86(2H,m), 9.05(1H, s), 9.16(1H, s), 9.32(1H,br.s), 9.45(1H,br.s)

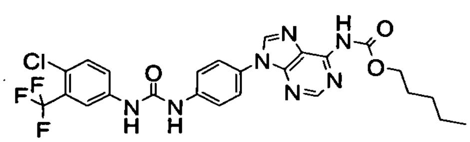
ESI (LC-MS positive mode) m/z 604 (M+H)

[Example 111]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid pentyl ester (Table 1, Compound No. 111)

[0550]

[Formula 154]



[0551]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and pentyl chloroformate by using the same method as in Example 107.

[0552]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.90(3H,t,J=6.9 Hz), 1.32-1.36(4H,m), 1.66(2H,dd,J=6.6, 7.3 Hz), 4.14(2H,t,J=6.6 Hz), 7.60-7.80(6H,m), 8.16(1H,d,J=2.7

Hz), 8.67(1H, s), 8.81(1H,s), 9.38(1H,br.s), 9.49(1H,br.s), 10.58(1H,br.s)

ESI (LC-MS positive mode) m/z 562 (M+H)

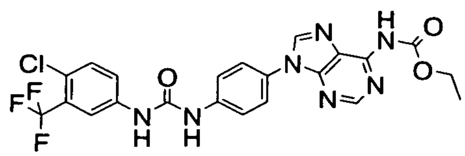
[Example 112]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid ethyl ester

(Table 1, Compound No. 112)

[0553]

[Formula 155]



[0554]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and ethyl chloroformate by using the same method as in Example 107.

[0555]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.28(3H,t,J=6.9 Hz), 4.19(2H,t,J=6.9 Hz), 7.62-7.82(6H,m), 8.15(1H,d,J=2.3 Hz), 8.68(1H,s), 8.82(1H,s), 9.32(1H,br.s), 9.45(1H,br.s), 10.58(1H,br.s)

ESI (LC-MS positive mode) m/z 520 (M+H)

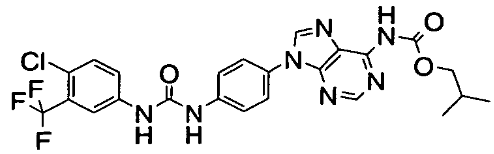
[Example 113]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid isobutyl ester

(Table 1, Compound No. 113)

[0556]

[Formula 156]



[0557]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and pentyl chloroformate by using the same method as in Example 107.

[0558]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.97(6H,d,J=6.6 Hz), 1.95(1H,m), 3.95(2H,d,J=6.6 Hz), 7.62-7.82(6H,m), 8.18(1H,br.s), 8.67(1H,s), 8.80(1H,s), 9.17(1H,br.s), 9.29(1H,br.s)

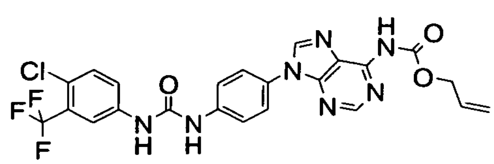
ESI (LC-MS positive mode) m/z 548 (M+H)

[Example 114]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid allyl ester (Table 1, Compound No. 114)

[0559]

[Formula 157]



[0560]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and allyl chloroformate by using

the same method as in Example 107.

[0561]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.69(2H,d,J=5.3 Hz), 5.27(1H,dd,J=2.0, 10.5 Hz), 5.44(1H,dd,J=2.0, 15.5 Hz), 6.00(1H,m), 7.62-7.82(6H,m), 8.17(1H,d,J=2.3 Hz), 8.68(1H,s), 8.83(1H,s), 9.49(1H,br.s), 9.60(1H,br.s, 10.84(1H,br.s)

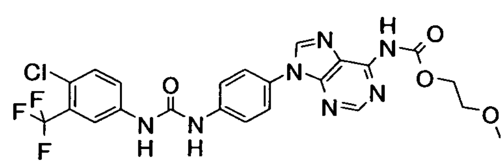
ESI (LC-MS positive mode) m/z 532 (M+H)

[Example 115]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid 2-methoxyethyl ester (Table 1, Compound No. 115)

[0562]

[Formula 158]



[0563]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and 2-methoxyethyl chloroformate by using the same method as in Example 107.

[0564]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.29(3H,s), 3.60(1H,d,J=4.6 Hz), 4.28(2H,d,J=4.6 Hz), 7.62-7.82(6H,m), 8.13(1H,d,J=2.0 Hz), 8.68(1H,s), 8.80(1H,s), 9.15(1H,br.s), 9.25(1H,br.s), 10.78(1H,br.s)

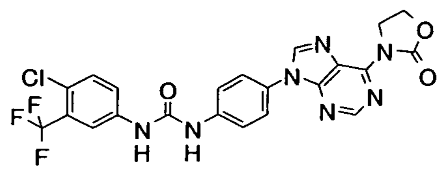
ESI (LC-MS positive mode) m/z 550 (M+H)

[Example 116]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-oxo-oxazolidin-3-yl)purin-9-yl]phenyl}urea (Table 1, Compound No. 116)

[0565]

[Formula 159]



[0566]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and 2-chloroethyl chloroformate by using the same method as in Example 107.

[0567]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.90(2H,t,J=5.3 Hz), 4.43(2H,t,J=5.3 Hz), 7.62-7.82(6H,m), 8.14(1H,d,J=2.0 Hz), 8.69(1H,s), 8.83(1H,s), 9.17(1H,br.s), 9.29(1H,br.s)

ESI (LC-MS positive mode) m/z 518 (M+H)

[Example 117]

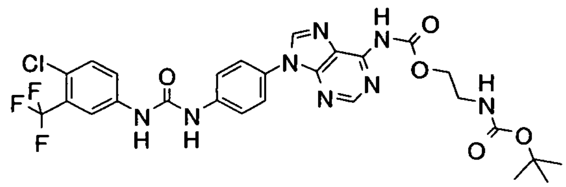
(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid 2-(methylamino)-ethyl ester hydrochloride (Table 1, Compound No. 117)

<u>Step A</u>

Preparation of (9-{4-[3-(4-chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-9H-purin-6-yl]carbamic acid 2-(tert-butoxycarbonylamino)ethyl ester

[0568]

[Formula 160]



[0569]

In 3 mL of methylene chloride, 110 mg (0.62 mmol) of (2-hydroxyethyl)-methylcarbamic acid tert-butyl ester and 108 μL (0.62 mol) of Hunig'a base were dissolved, and 74 mg (0.248 mmol) of triphosgene was added thereto at one time, and the mixture solution was stirred for 15 minutes. To the obtained solution, a solution obtained by dissolving 30 mg (0.062 mmol) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride in 3 mL of pyridine was added and the mixture solution was stirred at room temperature for three hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution, dried and concentrated. The residue was purified by Megabond Elute Silica Gel (1 g, methanol:ethyl acetate=1:30) to obtain 13 mg (33%) of (9-{4-[3-(4-chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-9H-purin-6-yl]carbamic acid 2-(tert-butoxycarbonylamino)ethyl ester as a white solid.

[0570]

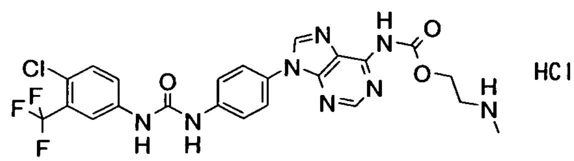
ESI (LC-MS positive mode) m/z 649 (M+H)

Step B

Preparation of (9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)carbamic acid 2-(methylamino)ethyl ester hydrochloride (Table 1, Compound No. 117)

[0571]

[Formula 161]



[0572]

In 2 mL of a 4N hydrogen chloride ethyl acetate solution, 13 mg (0.02 mmol) of (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl]carbamic acid 2-(tert-butoxycarbonylamino)ethyl ester was dissolved and the solution was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and then the residue was triturated with n-hexane:ethyl acetate=1:1, collected by filtration and vacuum dried to obtain 1.7 mg (16%) of (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl-carbamic acid 2-(methylamino)ethyl ester hydrochloride as a white solid.

[0573]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.85(3H,br.s), 4.37(2H,t,J=5.3 Hz), 7.62-7.81(6H,m), 8.08(1H.br.s), 8.14(1H,s), 8.71(1H,s), 8.88(1H,s), 9.60(1H,br.s), 9.82(1H,br.s)

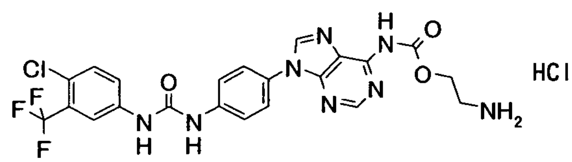
ESI (LC-MS positive mode) m/z 549 (M+H)

[Example 118]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid 2-aminoethyl ester hydrochloride (Table 1, Compound No. 118)

[0574]

[Formula 162]



[0575]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and (2-hydroxyethyl)carbamic acid tert-butyl ester by using the same techniques as in Example 117.

[0576]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.19(2H,m), 3.85(3H,br.s), 4.37(2H,t,J=5.3 Hz), 7.62-7.81(6H,m), 8.08(1H,.br.s), 8.14(1H,s), 8.71(1H,s), 8.88(1H,s), 9.60(1H,br.s), 9.82(1H,br.s)

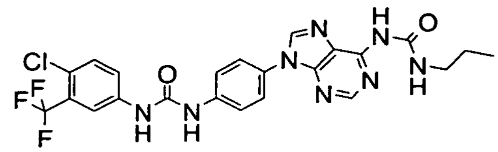
ESI (LC-MS positive mode) m/z 535 (M+H)

[Example 119]

1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl) ureido]phenyl}-9H-purin-6-yl)-3-propylurea (Table 1, Compound No. 119)

[0577]

[Formula 163]



[0578]

In 10 mL of pyridine, 300 mg (0.62 mmol) of 1-[4-(6-amino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride was dissolved, and 1.58 g (18.6 mmol) of propyl isocyanate was added thereto and the mixture solution was stirred at 50°C for eight hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution, dried and concentrated. The residue was triturated with n-hexane:ethyl acetate=1:1, collected by filtration and vacuum dried to obtain 210 mg (64%) of 1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)-3-propylurea (Table 1, Compound No. 119) as a white solid.

[0579]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.96(3H,t,J=7.2 Hz), 1.56(2H,q,J=7.3 Hz), 3.25(2H,m), 7.62-7.79(6H,m), 8.16(1H,d,J=2.3 Hz), 8.59(1H,s), 8.79(1H,s), 9.45(1H,br.s), 9.59(1H,br.s), 9.68(1H,br.s), 9.72(1H,br.s)

ESI (LC-MS positive mode) m/z 533 (M+H)

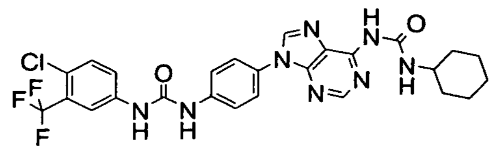
[Example 120]

1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-

ureido]phenyl}-9H-purin-6-yl)-3-cyclohexylurea (Table 1, Compound No. 120)

[0580]

[Formula 164]



[0581]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and cyclohexyl isocyanate by using the same techniques as in Example 119.

[0582]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.35(6H,m), 1.70(2H,m), 1.90(2H,m), 3.67(1H,m), 7.65-7.83(6H,m), 8.13(1H,d,J=2.0 Hz), 8.59(1H,s), 8.79(1H,s), 9.16(1H,s), 9.26(1H,s), 9.47(1H,br.s), 9.61(1H,s)

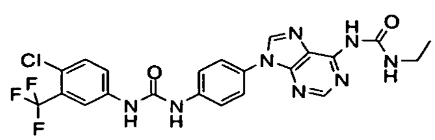
ESI (LC-MS positive mode) m/z 537 (M+H)

[Example 121]

1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-3-ethylurea (Table 1, Compound No. 121)

[0583]

[Formula 165]



[0584]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and ethyl isocyanate by using the same techniques as in Example 119.

[0585]

^{1}H-NMR (270 MHz, DMSO-d$_6$) δ (ppm): 1.17(3H,t,J=7.1 Hz), 3.30(2H,m), 7.62-7.80(6H,m), 8.13(1H,d,J=2.3 Hz), 8.59(1H,s), 8.79(1H,s), 9.15(1H,br.s), 9.26(1H,br.s), 9.39(1H,br.s), 9.66(1H,br.s)

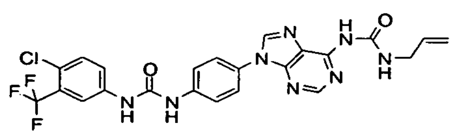
ESI (LC-MS positive mode) m/z 519 (M+H)

[Example 122]

1-Allyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea (Table 1, Compound No. 122)

[0586]

[Formula 166]



[0587]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and allyl isocyanate by using the same techniques as in Example 119.

[0588]

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 3.95(2H,m), 5.13(3H,d,J=10.0 Hz), 5.24(1H,d,J=17.2 Hz), 6.95(1H,m), 7.62-7.80(6H,m), 8.12(1H,d,J=2.4 Hz), 8.59(1H,s),

8.79(1H,s), 9.15(1H,br.s), 9.25(1H,br.s), 9.55(1H,br.s), 9.78(1H,br.s)

ESI (LC-MS positive mode) m/z 531 (M+H)

[0589]

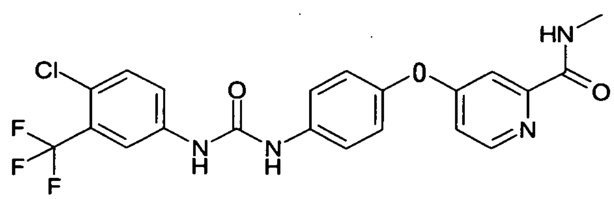
[Example B-1]

RAF-1 Enzyme Inhibition Test

With respect to the compounds relating to the present invention and the known compound (BAY 43-9006):

[0590]

[Formula 167]



the Raf-1 protein inhibition activity was measured. The enzymatic reaction was measured by incorporation of ^{33}P-phosphoric acid into MEK 1 protein by a recombinant Raf-1 protein. The activity was measured by preparing 50 μL of a reaction solution containing a dimethyl sulfoxide solution of the compound relating to the present invention or the compound BAY 43-9006 at a varied concentration [as the final concentration, the reaction solution containing 50 mL of TRIS hydrochloric buffer (pH 7.5), 1 mM of dithiothreitol, 100 mM of sodium chloride, 10 mM of potassium fluoride, 1 mM of sodium vanadate, 10 mM of magnesium chloride, 10 μM of adenosine triphosphate (ATP, containing ^{33}P-ATp of 12580Bq),2 μg of GST-MEK1 and 25 ng of an activated type GST-Raf-1]; keeping the reaction solution

at 30°C for 45 minutes; adding 100% trichloroacetic acid to the reaction solution in an amount twice the volume of the reaction solution to precipitate a proteinous component; recovering the precipitate on a glass filter; and measuring the radioactivity of the recovered product. The 50% inhibition concentration (IC_{50}) was obtained from the inhibition ratio to a sample-free reference.

[0591]

The compound BAT 43-9006 was prepared on the basis of the description (Example 41) of WO 00/42012. The results of measurement of Raf-1 inhibition activity are shown in Table 2.

[0592]

[Tanle 2]

Table 2

50% Enzyme Inhibition Concentration (IC_{50}value)/μM

Compound	Raf-1 Enzyme Inhibition
BAY43-9006	0.027
Compound 18	0.047
Compound 30	0.033
Compound 36	0.110
Compound 46	0.067
Compound 93	0.053
Compound 95	0.042
Compound 96	0.044
Compound 104	0.074
Compound 119	0.013

[0593]

As described in Table 2, the group of the compounds relating to the present invention has Raf-1 enzyme inhibition activity.

[Example B-2]

Cell Growth inhibition Test

With respect to the compounds relating to the present invention and the known compound (BAY 43-9006), cell growth inhibition activity was measured.

[0594]

A sample compound was in-series diluted with dimethyl sulfoxide, and then was 1/50 diluted with a Ca^{2+}- and Mg^{2+}-free phosphate-bufferized physiological saline and its 20 μL was poured to a 96-wel plate. Cell suspensions having 3,000 cells/180 μL were prepared with a culture medium obtained by adding 10% bovine fetal serum to McCoy's 5a medium in measuring the grow inhibition of human colorectal cancer cell strain HCT 116; a culture medium obtained by adding 10% bovine fetal serum, 30 μg/mL of vein endothelial cell growth auxiliary and 50 μg/mL of heparin to PRMI 1640 medium in measuring the grow inhibition of VEGF non-dependent human umbilical vein endothelial cells (HUVEC, purchased from Clonetics); and a culture medium obtained by adding 20 mg/mL of 10% bovine fetal serum and 20 ng/mL of VEGF to PRMI 1640 medium in measuring the grow inhibition of VEGF dependent HUVEC. Each of these cell suspensions was dividedly poured to the sample added plate in 180 μL/well and cultured in a 5% carbon dioxide incubator at 37°C. After 72 hours, 20 μL of WST-(HCT 116, a product of Dojin)

or WST-1 (HUVEC, a product of Roche diagnostics) was added thereto to each well and the absorbance at 450 nm (reference wavelength: 650 nm) was measured. From the growth inhibition ratio of addition of the sample compound to no-addition of the sample compound as a reference, the 50% growth inhibition IC_{50}) of the sample compound was calculated.

[0595]

With respect to the group of representative compounds of the present invention, the IC_{50} values of HCT 116 and HUVEC (VEGF nondependent growth and VEGF dependent growth) are shown in Table 3.

[0596]

[Table 3]

Table 3

50% Growth Inhibition Concentration (IC_{50}value)/μM

Compound	HUVEC (VEGF Nondependence)	HUVEC (VEGF Dependence)	HCT116
Bay43-9006	4.6	0.021	3.0
Compound 1	2.1	0.092	1.2
Compound 35	2.4	0.46	2.8
Compound 36	0.25	0.079	0.7
Compound 49	4.1	0.19	7.3
Compound 53	2.8	0.44	3.4
Compound 95	2.6	0.47	3.1
Compound 96	3.2	0.091	2.2
Compound 104	7.4	0.93	3.9
Compound 119	0.97	0.064	3.7

[0597]

As described in Table 3, the group of the compounds relating to the present invention has growth inhibition action on human colorectal caner strain HCT 116. Further, it has growth inhibition action on human umbilical vein endothelial cell (HUVEC).

[0598]

[Example B-3]

<u>Antitumor Test</u>

With respect to the compounds relating to the present invention and the known compound (BAY 43-9006), cell growth inhibition activity was measured.

A cell suspension of a human colorectal cancer cell strain HCT 116 was prepared with a Hunks' balanced salt solution. Its 5.0×10^6 were inoculated subcutaneously to the flank of each male Balb/c nude mouse. When the mean volume of a tumor reached 200 to 250 mm^3, a sample compound was orally administered one time a day for 5 days. The tumor volume was calculated from the calculation formula: $0.5\times(\text{minor diameter})^2\times(\text{major diameter})$, and the tumor growth inhibition ratio was calculated from the ratio of the tumor growth of the sample administered group to that of a reference group. The dosage in the antitumor test, the tumor growth inhibition ratio on the final administration day and the reduction in body weight on day 7 after starting administration are shown in Table 4.

[0599]

[Table 4]

Table 4 Antitumor Test

Compound	Dosage (mg/kg)	Tumor Inhibition Ratio (%)	Body Weight Reduction ratio (%)
Bay43-9006	100	83	17.0
Compound 36	200	81	5.9
Compound 93	200	79	6.0
Compound 119	200	89	8.5

[0600]

As described in Table 4, the group of the compounds relating to the present invention has antitumor activity and is safe with a small reduction in body weight.

[Example B-4]

[Method of Measuring Solubility to fasted state simulated intestinal fluid]

To a 96-well plate, 2 μL of a dimethyl sulfoxide solution of the compound relating to the present invention or that of the compound BAY 43-9006 was poured at one time, respectively, and fasted state simulated intestinal fluid (pH 6.5) was added 200 μL by 200 μL, and the plate was shaken at 37°C for 20 hours. The solution was filtered with a membrane filter and 101 μL of the filtrate was transferred to an UV plate, and 100 μL of a mixed solution of ethanol:water=2:1 was added thereto. On the other hand, as a standard solution, 2 μL of a dimethyl sulfoxide solution was added to a solution containing 4 μL of dimethyl sulfoxide, 400 μL of ethanol and 200 μL of water and the obtained solution was transferred 101 μL by 101 μL to the UV plate and to this UV plate, the simulated fasting

bile-containing intestinal juice (pH 6.5) was added 100 μL by 100 μL. The solubility was calculated by the following equation.

Solubility = (absorbance of sample solution-blank)/(absorbance of standard solution-blank)$\times$165 μL

wherein

165 μL is a concentration of the standard solution.

[Composition of fasted state simulated intestinal fluid]

Fasted state simulated intestinal fluid was prepared in accordance with E. Galia et al., Pharm. Res., 698, 1998.

[0601]

To about 90 mL of water, 161 mg of taurocholic acid, 59 mg of L-α-phosphatidylcholine, 0.39 g of potassium dihydrogenphosphate and 0.77 g of potassium chloride were added and the pH of the mixture solution was adjusted to 100 mL and the mixture solution was filtered with a membrane filter.

[0602]

The values relating to a representative group of the compounds of the present invention are shown in Table 5.

[0603]

Table 5

Solubility Test

Compound	Solubility (μg/mL)
BAY43-9006	10
Compound 21	24
Compound 34	34
Compound 35	24
Compound 36	22
Compound 92	76
Compound 96	102
Compound 109	39
Compound 115	19
Compound 119	39

[0604]

As described in Table 5, the group of the compounds relating to the present invention excels in the solubility in fasted state simulated intestinal fluid.

[Name of Document] Abstract

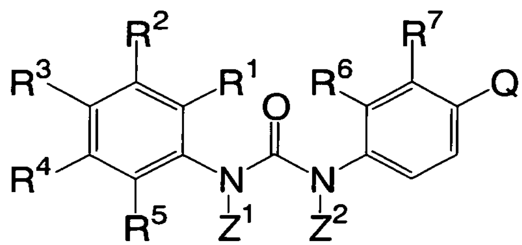
[Abstract]

[Problems] The present invention provides a compound useful as a preventive and therapeutic agent effective for diseases with phathologic angiogenesis.

[Measures of Solving the Problems]

According to the present invention, there is provided a compound represented by the formula (1):

[Formula 1]

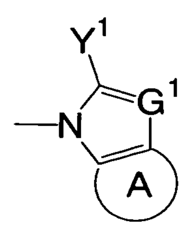


(1)

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a halogen atom, a halo C_1-C_6 alkyl group and a halo C_1-C_6 alkoxy group; R^6 and R^7 are each independently selected from a hydrogen atom and a halogen atom; Z^1 and Z^2 are each independently selected from a hydrogen atom, a hydroxyl group and $-O(CHR^{11})OC(=O)R^{12}$; Q is a group of the formula:

[Formula 2]



wherein G^1 is C-Y^2 or N; a ring A is a benzene ring or

a 5- to 6-membered unsaturated heterocycle; and the ring A may be substituted with one to three same or different substituents W;

a pharmaceutically acceptable salt thereof or a prodrug thereof.

[Selected Drawing] None.

[Name of Document] Patent Application

[Case No] 040227

[Filing Date] February 23, 2004

[To] Commissioner, Patent Office

[International Patent Classification]

C07D

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Nobuhiro OIKAWA

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Eisaku MIZUGUCHI

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Kenji MORIKAMI

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Nobuo SHIMMA

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Nobuya ISHII

[Inventor]

[Address] c/o CHUGAI SEIYAKU KABUSHIKI KAISHA of 200, Kajiwara, Kamakura-shi, Kanagawa

[Name] Toshiyuki TSUKAGUCHI

[Applicant for Patent]

[Identification No.] 000003311

[Appellation]	CHUGAI SEIYAKU KABUSHIKI KAISHA
[Proxy]	
[Identification No.]	100089705
[Address]	YUASA AND HARA, Section 206, New Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo
[Patent Attorney]	
[Name]	Ichio SHAMOTO
[Telephone]	03-3270-6641
[Facsimile]	03-3246-0233
[Proxy]	
[Identification No.]	100076691
[Patent Attorney]	
[Name]	Chuji MASUI
[Proxy]	
[Identification No.]	100075270
[Patent Attorney]	
[Name]	Yasushi KOBAYASHI
[Proxy]	
[Identification No.]	100080137
[Patent Attorney]	
[Name]	Akio CHIBA
[Proxy]	
[Identification No.]	100096013
[Patent Attorney]	
[Name]	Hiroyuki TOMITA
[Fees]	
[Page No. of Books]	051806
[Amount]	¥21,000.-
[List of the Documents]	

[Item]	Claims	1
[Item]	Specification	1
[Item]	Abstract	1

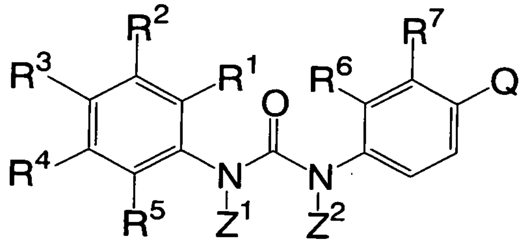
[General Power of Attorney No.] 0107764

[Name of Document] Claims

[Claim 1]

A compound represented by formula (1):

[Formula 1]



(1)

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group which may be substituted with one or more halogen atoms and a C_1-C_6 alkoxy group which may be substituted with one or more halogen atoms;

R^6 and R^7 are each independently selected from a hydrogen atom and a halogen atom;

Z^1 and Z^2 are each independently selected from a hydrogen atom, a hydroxyl group and $-O(CHR^{11})OC(=O)R^{12}$;

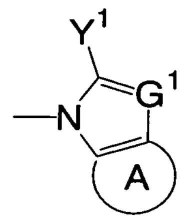
wherein

R^{11} is a hydrogen atom or a C_1-C_6 alkyl group; and

R^{12} is a pyrrolidinyl group, a piperidinyl group, a morpholinyl group, a piperazinyl group, an amino C_1-C_6 alkyl group, a mono- or di(C_1-C_6 alkyl)amino C_1-C_6 alkyl group, an amino C_1-C_6 alkylamino group or a mono- or di(C_1-C_6 alkyl)-amino C_1-C_6 alkylamino group;

Q is a group of the formula:

[Formula 2]



wherein

G^1 is $C\text{-}Y^2$ or N;

ring A is a benzene ring or a 5- to 6-membered unsaturated heterocycle; a nitrogen atom present in the heterocycle may be an N-oxide; and the ring A may be substituted with one to three same or different substituents W;

Y^1 and Y^2 are each independently selected from a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxy C_1-C_6 alkyl group, a C_1-C_6 alkoxy C_1-C_6 alkoxy group, an amino C_1-C_6 alkoxy group, a (C_1-C_6 alkyl)amino C_1-C_6 alkyl group, an amino group, a (C_1-C_6 alkyl)amino group and a di(C_1-C_6 alkyl)amino group;

W is a halogen atom, a nitro group, a cyano group, a hydroxyl group, -NRaRb, -N=C(-Rc)NRaRb, -CONRaRb, -OC(=O)NRaRb, $-SO_2NRaRb$, -N(-Ra)C(=O)NRa'Rb', -N(-Ra)C(=O)ORd, -N[C(=O)ORd][C(=O)ORd'], -C(=O)ORd, $-S(=O)_m-Rd$, -O-Rd, -OC(=O)Rc, -N(-Ra)C(=O)Rc, -N[C(=O)Rc][C(=O)Rc'], $-N(-Ra)SO_2Rc$, $-N(SO_2Rc)(SO_2Rc')$, -C(=NORd)NRa'Rb', -C(=NRa)NRa'Rb', -C(=NORa)Rc, -C(=O)Rc, a C_1-C_6 alkyl group which may be substituted with one or more Y^3,

a C_2-C_7 alkenyl group which may be substituted with one or more Y^3, a C_2-C_7 alkynyl group which may be substituted with one or more Y^3, an aryl group which may be substituted with one or more Y^3 or a heteroaryl group which may be substituted with one or more Y^3;

Ra, Ra', Rb, Rb', Rc, Rc', Rd and Rd' are each independently selected from a hydrogen atom, a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, $-[(C_1$-C_6 alkylene$)-O]_n-(C_1$-C_3 alkyl$)$, an aryl group or a heteroaryl group, a pyrrolidinyl group and a pyperidinyl group (wherein the pyrrolidinyl group or the pyperidinyl group may be substituted with a C_1-C_3 alkyl group); or

Ra and Rb, Ra' and Rb', Ra and Rd, Ra and Ra', Ra and Rc, Rc and Rc' or Rd and Ra' may form a saturated or unsaturated 5- to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

Ra, Rb, Ra', Rb', Rc, Rc', Rd and Rd' each may be substituted with one to three same or different substituents selected from Y^3;

m is an integer selected from 0 to 2;

n is an integer selected from 1 to 4;

Y^3 is a halogen atom, -NRxRy, -C(=O)ORz, -ORz, -CONRxRy, -OC(=O)NRxRY, $-SO_2NRxRy$, -N(-Rx)C(=O)NRx'Ry', -N(-Rx)C(=O)ORz, -S-Rz,

-SO-Rz, $-SO_2$-Rz, -OC(=O)Rz, -N(Rx)C(=O)Rz,

-C(=NORz)NRx′Ry′, -C(=NRx)NRx′Ry′, -C(=NORx)Rz,

-[O-(C_1-C_6 alkylene)]$_n$-O(C_1-C_3 alkyl), -N(-Rx)-(C_1-C_6 alkylene)-O(C_1-C_3 alkyl), -CORz, a C_1-C_6 alkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, an aryl group or a heteroaryl group;

Rx, Rx′, Ry, Ry′ and Rz are each independently selected from a hydrogen atom and a C_1-C_4 alkyl group;

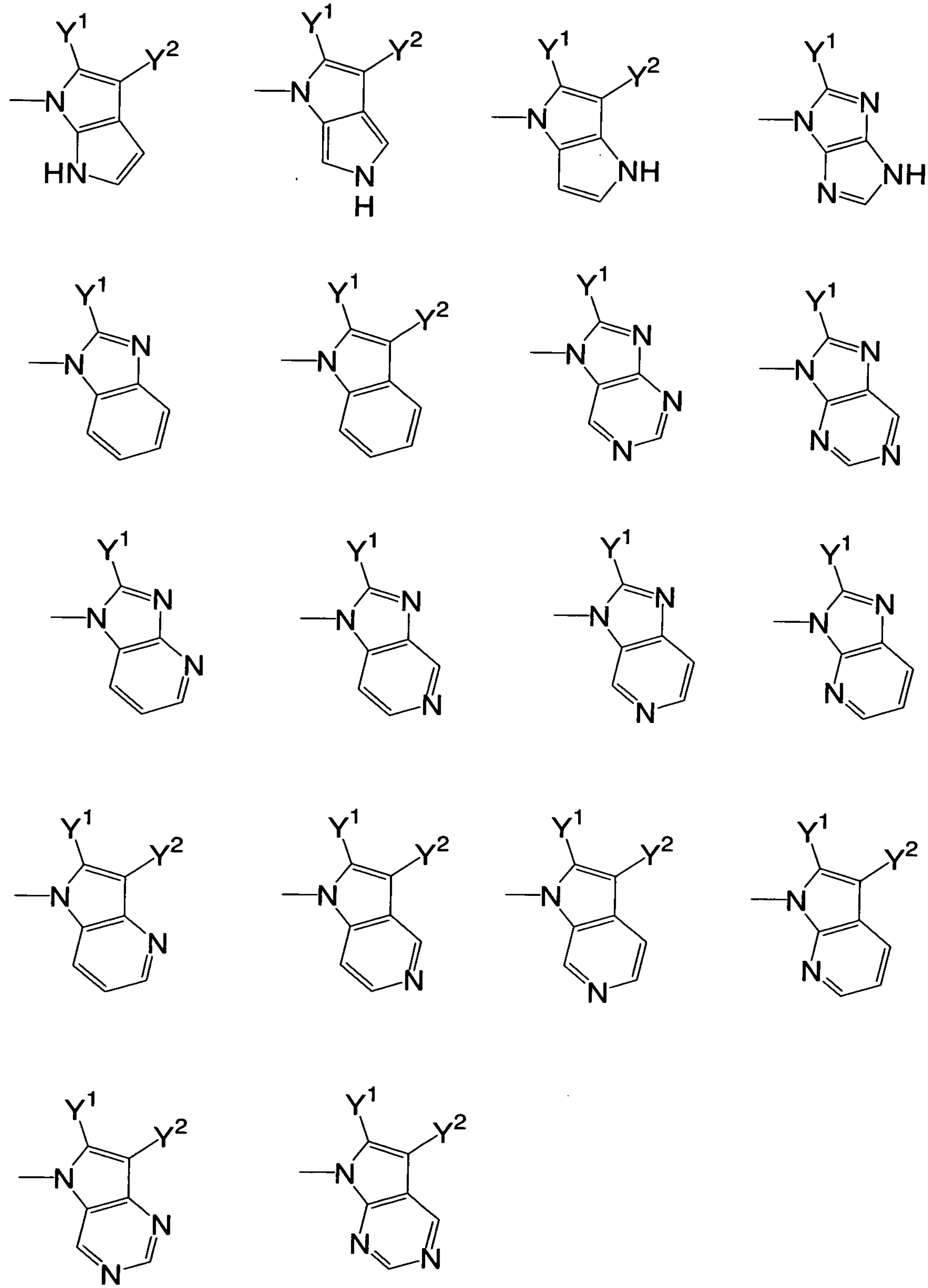
Rx and Ry, Rx and Rx′, Rx and Rz or Rz and Rx′ may form a saturated or unsaturated 5-to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

a pharmaceutically acceptable salt thereof or a prodrug thereof.

[Claim 2]

The compound of claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein Q is a group of the formula selected from:

[Formula 3]



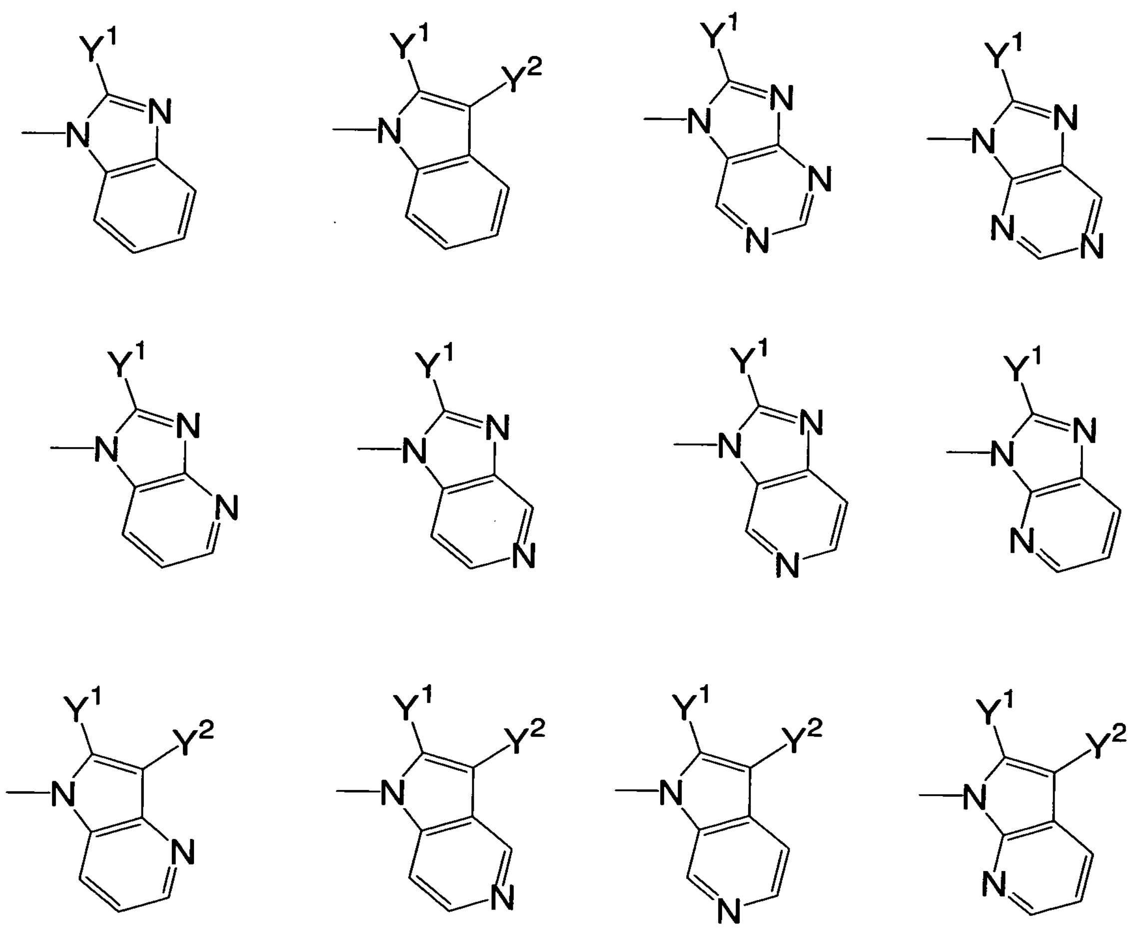
which may be substituted with one to three same or

different substituents W.

[Claim 3]

The compound of claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein Q is a group of the formula selected from:

[Formula 4]

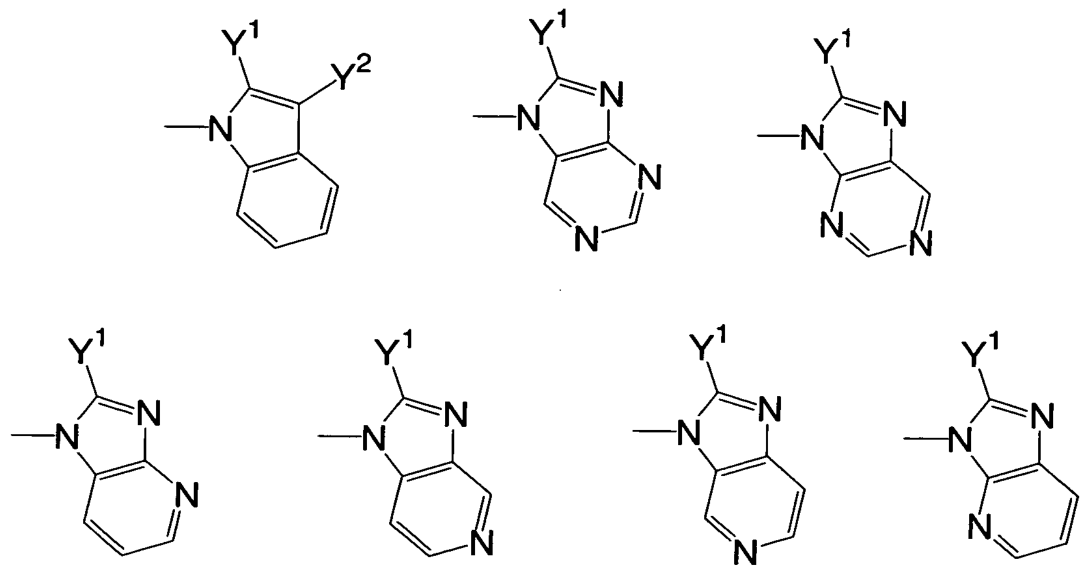


which may be substituted with one to three same or different substituents W.

[Claim 4]

The compound of claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein Q is a group of the formula selected from:

[Formula 5]



which may be substituted with one to three same or different substituents W.

[Claim 5]

The compound of any one of claims 1 to 4, a pharmaceutically acceptable salt thereof or a prodrug thereof,

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a chlorine atom, a fluorine atom, a bromine atom and a trifluoromethyl group;

R^6 and R^7 are hydrogen atoms; and

Z^1 and Z^2 are each independently selected from a hydrogen atom, and a hydroxyl group.

[Claim 6]

A compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1 which has Raf inhibiting effect and angiogenesis inhibiting effect and is

used for treating cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes.

[Claim 7]

A pharmaceutical composition comprising a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of any one of claims 1 to 5 as an active ingredient.

[Claim 8]

An Raf inhibitor or an angiogenesis inhibitor comprising a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of any one of claims 1 to 5 as an active ingredient.

[Claim 9]

A preventive or therapeutic agent for a disease selected from cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes which comprises a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof of any one of claims 1 to 5 as an active ingredient.

[Name of Document] Specification

[Title of Invention] HETEROARYL PHENYLUREA DERIVATIVES

[Technical Field to which the Invention Pertains]

[0001]

The present invention relates to a novel heteroaryl phenylurea derivative, a pharmaceutically acceptable salt thereof, a synthetic intermediate of the derivative and a pharmaceutical composition comprising the derivative or its pharmaceutically acceptable salt.

[0002]

Particularly, the present invention relates to a compound useful as a Raf inhibitor and an angiogenesis inhibitor. The above-described compound is useful for treating growth diseases, for example, cancer, psoriasis or atherosclerosis and is also useful for treating chronic rheumatoid arthritis and diabetes.

[Background Art]

[0003]

The Ras signal transduction pathway responds to various extracellular signals, for example, growth factors, cytokines and an extracellular matrix (ECM) through the cell-surface receptors to play an important role in proliferation, differentiation and transformation of cells.

[0004]

The activation of the Ras protein in normal cells begins by the interaction of such extracellular signals as growth facters with the cell-surface receptors, and then the activated Ras protein interacts with Raf, a serine-

threonine protein kinase, to activate Raf (see Non-patent Document 1 and Non-patent Document 2). It is known that with Raf, there are three types of isoforms of A-Raf of 68 Kd, B-Raf of 95 and Raf-1 (c-Raf) of 74 Kd, and each is different in the aspects of the interaction with the Ras protein, the capacity of activating the substrate MEK, the expression and distribution in organs and the like, and the study with the use of a knockout mouse shows that all three A-Raf, B-Raf and Raf-1 are essential in survival. The activated Raf successively activates the substrate MEK by phosphorylation and the activated MEK activates ERK 1 and ERK 2 (MAPK). The activated ERK finally activates various substrates such as transcription factors in the cell nucleus and cytoplasma to bring about cellular changes (proliferation, differentiation and transformation) in response to the extracellular signals. These cellular changes including proliferation in normal cells are appropriately regulated but it is observed that in human cancer cells, about 20% of the Ras protein is always mutated to be in an activated state (GTP complex) and it is known that as a result, the growth signal to the Raf/MEK/ERK cascade is maintained to play an important role in the growth of human cancer cells (see Non-patent Document 3). Further, in the recent study, it is reported that the mutation of B-raf is confirmed in 66% of melanormas, 15% of colon cancers and 14% of liver cancers, and the Raf/MEK/ERK cascade is in an activated state (see Non-patent Document 4).

[0005]

In addition to the role as a direct downstream effector of the Ras protein in the Raf/MEK/ERK cascade as described above, the Raf kinase is known to play a key role in controlling the apoptosis of cells by various mechanisms (see Non-patent Document 5).

[0006]

Thus, the techniques of blocking the Ras signal transduction pathway which plays an important role in the proliferation of cancer cells by inhibiting the Raf kinase as a target can be thought useful. Actually, it is reported that by inhibiting the expression of Raf with the RNA antisense, the growth of various human cancers is inhibited in vitro and in vivo (see Non-patent Document 6).

[0007]

Tumor cells take in oxygen and nutrients necessary for survival and growth from the surrounding environment. In a solid tumor, these substances are supplied by simple diffusion until the solid cancer reaches a certain size. However, as the solid tumor grows to form a region 1 to 2 mm or more apart from the nearest blood vessel, this region forms a hypoxia region where the oxygen concentration is low, the nutrients are poor and the pH is low. Against to these stresses, tumor cells respond by various angiogenesis factors to stimulate the formation of a new blood vessel from the neighboring vascular endothelial cells. The angiogenesis thus started is thought to be essential in the growth of the solid tumors. There are a number of reports

which suggests the relationship between VEGF (vascular endothelial growth factor), a growth factor specific for the vascular endothelial cells and cancers, and the drugs which target VEGF or the tyrosine kinase activity of its receptors have recently been developed (see Non-patent Document 7 and Non-patent Document 8). Up to now, it is known that VEGF bonds to three types of receptor tyrosine kinases of VEGFR-1 (flt-1), VEGFR-2 (KDR) and VEGF-3 (Flt-4), and since KDR performs strongly ligand-dependent autophosphorylation, KDR is thought to be essential to VEGF-dependent biological responses including angiogenesis.

[0008]

On the other hand, a number of factors which anticipate in angiogenesis are known in addition to VEGF, and the development of inhibitors of such growth fators which play a key role in angiogenesis and specifically act on vascular endothelial cells to inhibit their growth and functions is strongly desired as therapeutic agents for angiogenic diseases such as cancers.

[0009]

With respect to the relationship between the two cancer treatment targets, that is, Raf and angiogenesis, an interesting report has recently been made. The activation of B-Raf and Raf-1 depends on not only the Ras protein but also growth factor signals. Basic fibroblast growth factor (b-FGF) activates Raf-1 through PAK-1 (p21-activated protein kinase-1) by the phosphorylation of serine 338 and 339 non-dependently to MEK 1 to protect endothelial cells

from apoptosis. The VEGF signal activates Raf-1 through Src kinase by phosphorylation of tyrosine 340 and 341 dependently to MEK 1 to protect endothelial cells. By this report, it has been clarified that Raf plays a key role in not only the growth of cancer cells but also the control of survival of endothelial cell on angiogenesis (see Non-patent Document 9).

[0010]

Further, angiogenesis is a physiological phenomenon essential in embryonic formation of the fetal period, wound healing of an adult, the menstrual period of an adult female and the like but it is reported that abnormality of angiogenesis in an adult individual relates to psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetic diseases (see Non-patent Document 10 and Non-patent Document 11), and inhibition of angiogenesis is useful for treating these diseases with the abnormality of angiogenesis.

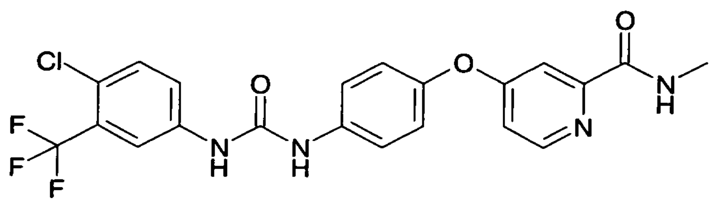
[0011]

Heretofore, a number of urea compounds which exhibit anticancer action by inhibiting any of Raf and kinases relating to angiogenesis (see Patent Documents 1 to 12). However, these compounds have a problem of solubility in water due to the high hydrophobicity and high crystallinity attributed to the phenylurea skeleton. Particularly in the case of oral drugs, the property of inferior solubility in water tents to lead to severe problems in clinical development such as poor bioavailability, unstable effecacy

due to the individual difference in PK among patients or tendency of accumulation (see Non-patent Document 11 and Non-patent 13). For example, it is reported that the following compound Bay 43-9006 (Patent Document, Example 41):

[0012]

[Formula 1]



[0013]

is a Raf-1 and B-RAF inhibitor and is also an inhibitor of kinases relating to the angiogenesis and the progression of a cancer including KDR, VEGFR-3, Flt-3, c-KIT and PDGFR-β (see Non-patent Document 15). However, the results of the phase I clinical study of the compound are reported (see Non-patent Document 15) and the compound is pointed out to have problems of high interpatient PK variability, tendency of accumulation upon multiple dosing and the like due to high lipophilicity and low water solubility.

[Patent Document 1] International Publication No.98/52559 Pamphlet

[Patent Document 2] International Publication No.99/32106 Pamphlet

[Patent Document 3] International Publication No.99/32436 Pamphlet

[Patent Document 4] International Publication No.99/32455 Pamphlet

[Patent Document 5] International Publication No.00/42012 Pamphlet

[Patent Document 6] International Publication No.02/62763 Pamphlet

[Patent Document 7] International Publication No.02/85857 Pamphlet

[Patent Document 8] International Publication No.03/47579 Pamphlet

[Patent Document 9] International Publication No.03/68223 Pamphlet

[Patent Document 10] International Publication No.03/40228 Pamphlet

[Patent Document 11] International Publication No.03/40229 Pamphlet

[Patent Document 12] International Publication No.03/68746 Pamphlet

[Non-patent Document 1] Trends Biochem. Sci., Vol.19, 474-480, 1994

[Non-patent Document 2] Science, Vol.264, 1463-1467, 1994

[Non-patent Document 3] Annual Reports in Medicinal Chemistry, Vol.29, 165-174, 1994

[Non-patent Document 4] Nature, Vol.417, 949, 2002

[Non-patent Document 5] Biochemical Pharmacology, Vol.66, 1341-1345, 2003

[Non-patent Document 6] Nature, Vol.349, 426-429, 1991

[Non-patent Document 7] J. Clinical Oncology, Vol.21, 60-65,

2003

[Non-patent Document 8] Expert Opinion Investigational Drugs, Vol.12, 51-64, 2003,

[Non-patent Document 9] Science, Vol.301, 94-96, 2003

[Non-patent Document 10] New England Journal of Medicine, Vol.333(26), 1757-63, 1995

[Non-patent Document 11] Angiogenesis, Vol.5(4), 237-256, 2002

[Non-patent Document 12] Pharmazeutische Industrie, Vol.64(8), 800-807, 2002

[Non-patent Document 13] Pharmazeutische Industrie Vol.64(9), 985-991, 2002

[Non-patent Document 14] AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Proceedings, p.69, No.A78, 2003

[Non-patent Document 15] American Society of Clinical Oncology, Annual Meeting (May 18 to May 21, 2002) Abstracts, Nos. 121, 1816 and 1916, 2002.

[Disclosure of the Invention]

[Problems to be Solved by the Invention]

[0014]

The present invention has an object to provide a compound which has high Raf inhibition activity and angiogenesis inhibition activity and is useful as an effective therapeutic and preventive agent for a disease with pathologic angiogenesis, for example, cancer and

metastasis of cancer, its preparation method, an intermediate useful for its preparation and furthermore pharmaceutical composition containing these compounds.

Means to Solve the Problem.

[Measures of Solving the Problems]

[0015]

As the results of strenuously developing heteroaryl phenylurea derivatives having excellent Raf and angio-genesis inhibition effects by the present inventors, it has been found that derivatives having a specified structure not only exhibit excellent both inhibition actions but also excel in solubility to water and shows high and stable oral bioavailability and are useful as preventive or therapeutic agents excellent in safety for proliferative diseases, and the present invention has been completed.

[0016]

Compared to BAY 43-9006 disclosed in Patent Document 5 (international Publication No. 00/42012 Pamphlet), the compounds of the present invention have excellent solubility in water. Therefore, the compounds of the present invention are expected to have less interpatient variability in PK parameters such as Cmax, AUC value and half-life, and excellent and stable oral absorption, when administered orally. Further, the compounds of the present invention cause less body weight reduction in a dosage to exhibit the same therapeutic effect as BAY 43-9006 in an animal model and accordingly are useful as safer therapeutic or preventive agents (therapeutic agents,

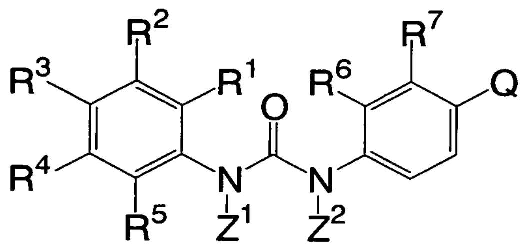
especially).

[0017]

Namely, according to one aspect of the present invention, there is provided a compound represented by formula (1):

[0018]

[Formula 2]



(1)

[0019]

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group which may be substituted with one or more halogen atoms and a C_1-C_6 alkoxy group which may be substituted with one or more halogen atoms;

R^6 and R^7 are each independently selected from a hydrogen atom and a halogen atom;

Z^1 and Z^2 are each independently selected from a hydrogen atom, a hydroxyl group and -$O(CHR^{11})OC(=O)R^{12}$;

wherein

R^{11} is a hydrogen atom or a C_1-C_6 alkyl group; and

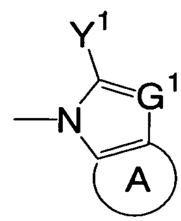
R^{12} is a pyrrolidinyl group, a piperidinyl group, a morpholinyl group, a piperazinyl group, an amino C_1-C_6 alkyl group, a mono- or di(C_1-C_6 alkyl)amino C_1-C_6

alkyl group, an amino C_1-C_6 alkylamino group or a mono- or di(C_1-C_6 alkyl)-amino C_1-C_6 alkylamino group;

Q is a group of the formula:

[0020]

[Formula 3]



[0021]

wherein

G^1 is C-Y^2 or N;

ring A is a benzene ring or a 5- to 6-membered unsaturated heterocycle; a nitrogen atom present in the heterocycle may be an N-oxide; and the ring A may be substituted with one to three same or different substituents W;

Y^1 and Y^2 are each independently selected from a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxy C_1-C_6 alkyl group, a C_1-C_6 alkoxy C_1-C_6 alkoxy group, an amino C_1-C_6 alkoxy group, a (C_1-C_6 alkyl)amino C_1-C_6 alkyl group, an amino group, a (C_1-C_6 alkyl)amino group and a di(C_1-C_6 alkyl)amino group;

W is a halogen atom, a nitro group, a cyano group, a hydroxyl group, -NRaRb, -N=C(-Rc)NRaRb, -CONRaRb, -OC(=O)NRaRb, $-SO_2NRaRb$, -N(-Ra)C(=O)NRa′Rb′, -N(-Ra)C(=O)ORd, -N[C(=O)ORd][C(=O)ORd′],

$-C(=O)ORd$, $-S(=O)_m-Rd$, $-O-Rd$, $-OC(=O)Rc$, $-N(-Ra)C(=O)Rc$, $-N[C(=O)Rc][C(=O)Rc']$, $-N(-Ra)SO_2Rc$, $-N(SO_2Rc)(SO_2Rc')$, $-C(=NORd)NRa'Rb'$, $-C(=NRa)NRa'Rb'$, $-C(=NORa)Rc$, $-C(=O)Rc$, a C_1-C_6 alkyl group which may be substituted with one or more Y^3, a C_2-C_7 alkenyl group which may be substituted with one or more Y^3, a C_2-C_7 alkynyl group which may be substituted with one or more Y^3, an aryl group which may be substituted with one or more Y^3 or a heteroaryl group which may be substituted with one or more Y^3;

Ra, Ra', Rb, Rb', Rc, Rc', Rd and Rd' are each independently selected from a hydrogen atom, a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, $-[(C_1$-C_6 alkylene$)-O]_n-(C_1$-C_3 alkyl$)$, an aryl group or a heteroaryl group, a pyrrolidinyl group and a pyperidinyl group (wherein the pyrrolidinyl group or the pyperidinyl group may be substituted with a C_1-C_3 alkyl group); or

Ra and Rb, Ra' and Rb', Ra and Rd, Ra and Ra', Ra and Rc, Rc and Rc' or Rd and Ra' may form a saturated or unsaturated 5- to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

Ra, Rb, Ra', Rb', Rc, Rc', Rd and Rd' each may be substituted with one to three same or different substituents selected from Y^3;

m is an integer selected from 0 to 2;

n is an integer selected from 1 to 4;

Y^3 is a halogen atom, -NRxRy, -C(=O)ORz, -ORz, -CONRxRy, -OC(=O)NRxRY, -SO_2NRxRy, -N(-Rx)C(=O)NRx′Ry′, -N(-Rx)C(=O)ORz, -S-Rz, -SO-Rz, -SO_2-Rz, -OC(=O)Rz, -N(Rx)C(=O)Rz, -C(=NORz)NRx′Ry′, -C(=NRx)NRx′Ry′, -C(=NORx)Rz, -[O-(C_1-C_6 alkylene)]$_n$-O(C_1-C_3 alkyl), -N(-Rx)-(C_1-C_6 alkylene)-O(C_1-C_3 alkyl), -CORz, a C_1-C_6 alkyl group, a C_2-C_8 alkyenyl group, a C_2-C_8 alkynyl group, an aryl group or a heteroaryl group;

Rx, Rx′, Ry, Ry′ and Rz are each independently selected from a hydrogen atom and a C_1-C_4 alkyl group;

Rx and Ry, Rx and Rx′, Rx and Rz or Rz and Rx′ may form a saturated or unsaturated 5-to 6-membered heterocycle by ring-closing at the bonding position of each of these two groups;

a pharmaceutically acceptable salt thereof or a prodrug thereof.

[0022]

In the above-described formula (1), Y^2 is preferably a hydrogen atom. Further, R^{11} is preferably a hydrogen atom or a methyl group, and R^{12} is preferably a pyrrolidinyl group or a piperazinyl group.

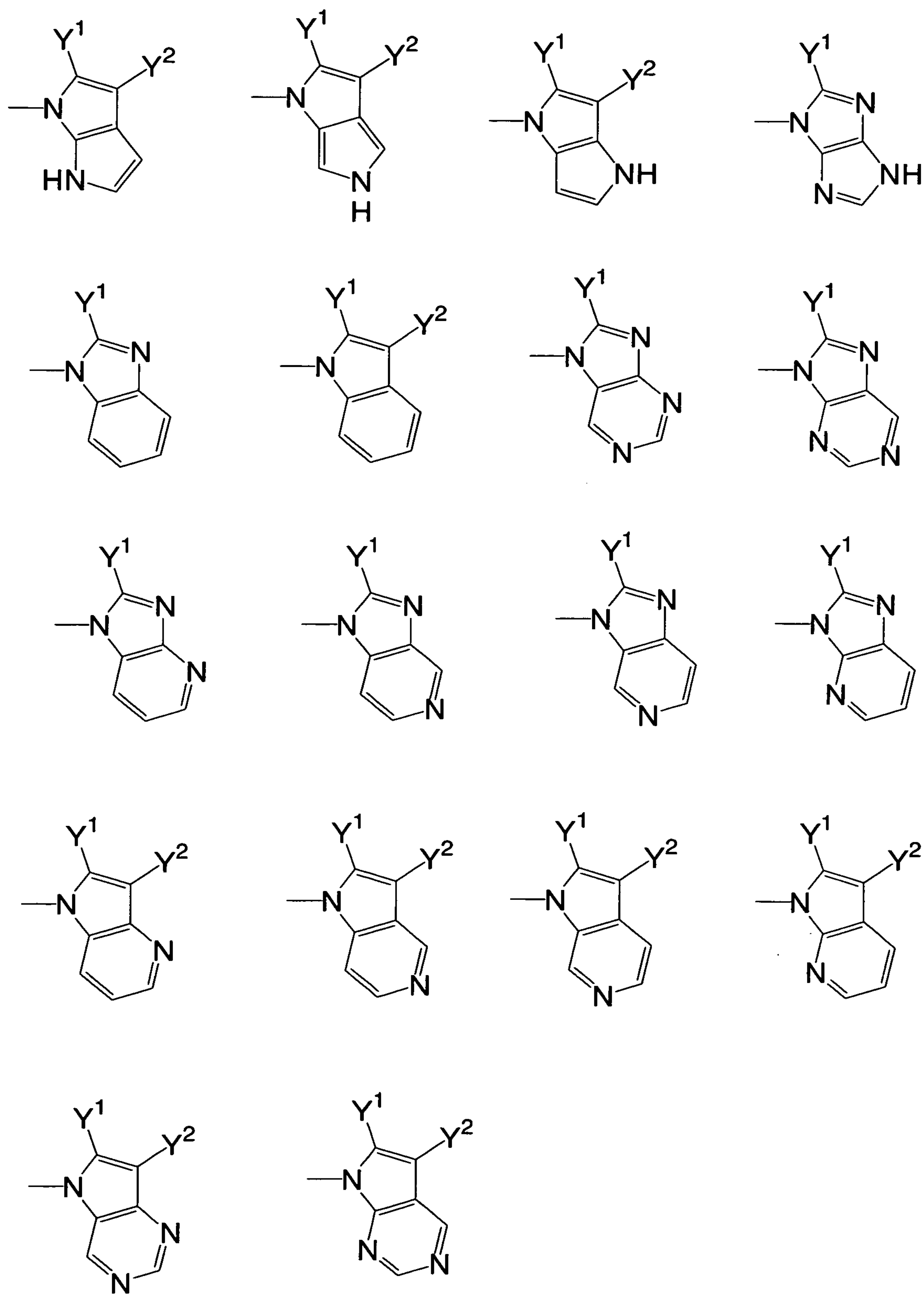
[0023]

According to another aspect of the present invention, there is provided a compound of formula (1), a

pharmaceutically acceptable salt thereof or a prodrug thereof wherein Q is a group of the formula selected from:

[0024]

[Formula 4]



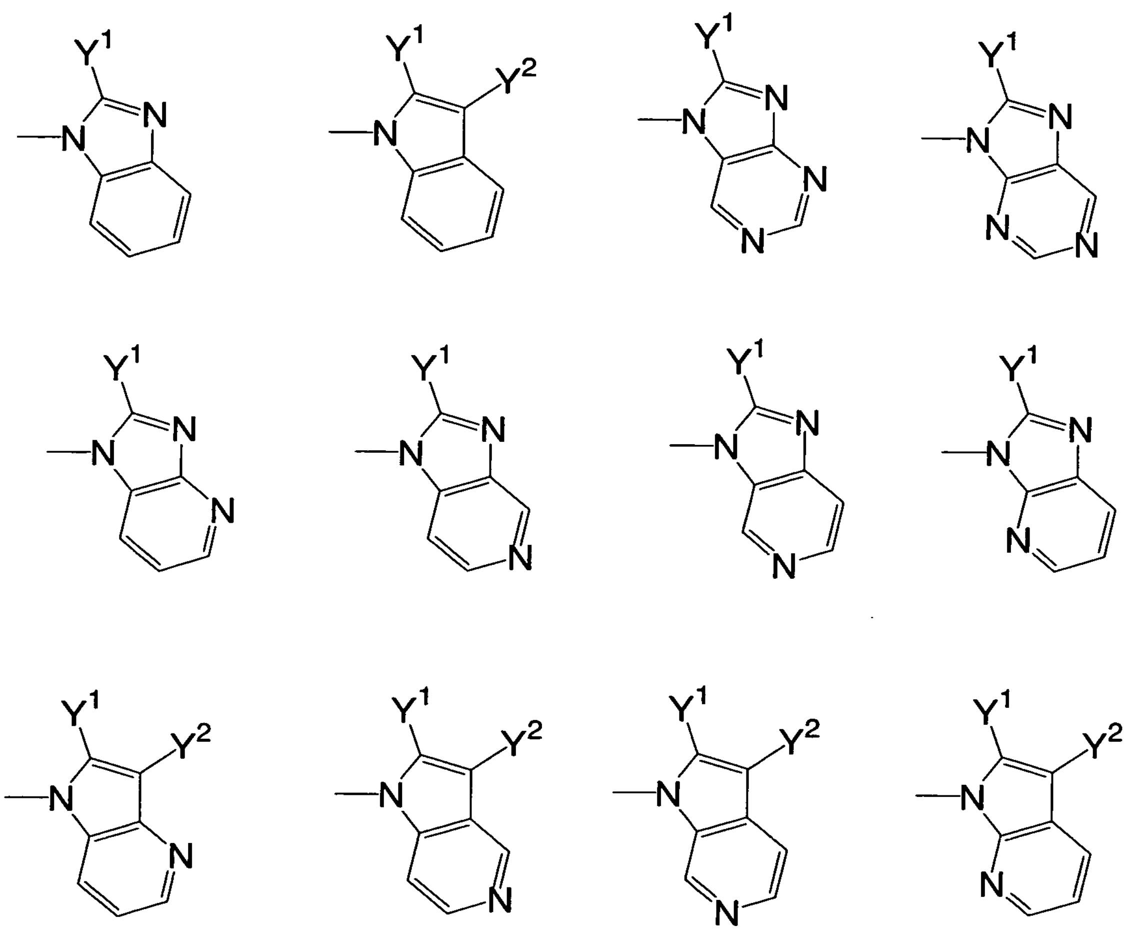
[0025]

which may be substituted with one to three same or different substituents W.

[0026]

Herein, Q may be a group of the formula selected from:

[Formula 5]



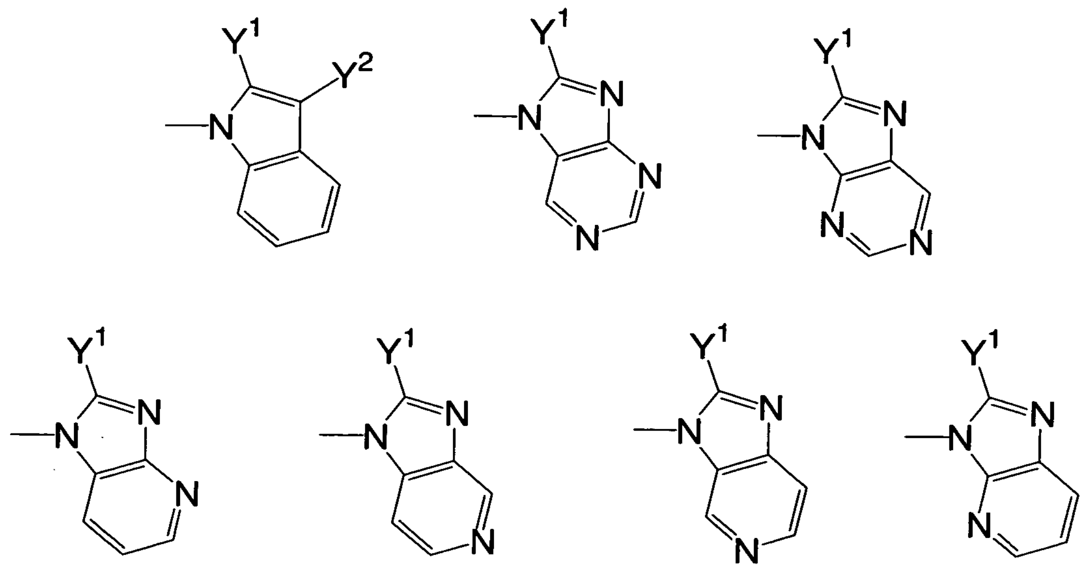
[0027]

which may be substituted with one to three same or different substituents W.

Further, Q may be a group of the formula selected from:

[0028]

[Formula 6]



[0029]

which may be substituted with one to three same or different substituents W.

According to a further aspect of the present invention, there is provided a compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof, wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a chlorine atom, a fluorine atom, a bromine atom and a trifluoro-methyl group;

R^6 and R^7 are hydrogen atoms; and

Z^1 and Z^2 are each independently selected from a hydrogen atom and a hydroxyl group.

[0030]

According to another aspect of the present invention, the above-described compound of formula (1), a

pharmaceutically acceptable salt thereof or a prodrug thereof which has Raf inhibition and angiogenesis inhibition actions and is used in treating a cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes is provided.

[0031]

According to a further aspect of the present invention, a pharmaceutical composition comprising the above-described compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof as an active ingredient is provided.

[0032]

According to a still further aspect of the present invention, a Raf inhibitor or an angiogenesis inhibitor comprising the above-described compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof as an active ingredient is provided.

[0033]

According to a further aspect of the present invention, a preventive or therapeutic agent for a disease selected from cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes which contains the above-described compound of formula (1), a pharmaceutically acceptable salt thereof or a prodrug thereof as an active ingredient is provided.

[Embodiments of the Invention]

[0034]

The term "halogen", as used in the present invention,

means a fluorine atom, a chlorine atom, a bromine atom and iodine atom.

The term "C_1-C_3 alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 3 carbon atoms and includes, for example, methyl, ethyl, n-propyl and i-propyl.

[0035]

The term "C_1-C_4 alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms and include, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butly, sec-butyl and tert-butyl.

[0036]

The term "C_1-C_6 alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms and includes, for example, "C_1-C_4 alkyl group" such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl and t-butyl, and further includes n-pentyl, 3-methylbutyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3-ethylbutyl and 2-ethylbutyl.

[0037]

The term "C_1-C_{10} alkyl group", as used in the present invention, means a straight-chain or branched-chain alkyl group having 1 to 10 carbon atoms and includes, for example, "C_1-C_4 alkyl group" and "C_1-C_6 alkyl group", and further includes n-heptyl, n-octyl, n-nonyl and n-decanyl.

[0038]

The term "C_3-C_8 cycloalkyl group", as used in the present invention, means as cyclic or partially cyclic alkyl group having 3 to 8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, hexylcyclo-methyl, cyclo-propyl substituted with a C_1-C_5 alkyl, cyclopentyl substituted with a C_1-C_3 alkyl group and cyclohexyl substituted with a C_1-C_2 alkyl group.

[0039]

The term "C_1-C_6 alkoxy group", as used in the present invention, means an alkyloxy group having a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms as an alkyl moiety and includes, for example, methoxy, n-propoxy, i-propoxy, n-butoxy, s-butyoxy, i-butoxy, t-butoxy, n-pentoxy, 3-methylbutoxy, 2-methylbutoxy, 1-methylbutoxy, 1-ethylpropoxy, n-hexyloxy, 4-methylpentoxy, 3-methyl-pentoxy, 2-methylpentoxy, 1-methylpentoxy, 3-ethylbutoxy and 2-ethylbutoxy.

[0040]

The term "C_2-C_8 alkenyl group", as used in the present invention, means a straight-chain or branched-chain alkenyl group having 2 to 8 carbon atoms and include, for example, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), propen-2-yl and 3-butenyl (homoallyl).

[0041]

The term "C_2-C_8 alkynyl group", as used in the present invention, means a straight-chain or branched-chain alkynyl

group having 2 to 8 carbon atoms and include, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl.

[0042]

The term "aryl group", as used in the present invention, means a C_6-C_{10} aromatic hydrocarbon group and include, for example, aphenyl, 1-naphthyl and 2-naphthyl.

The term "heteroaryl group", as used in the present invention, means a 5- to 10-membered aromatic heterocyclyl group containing one or more heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom and include, for example, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl and quinolyl. The substituting position of the heteroaryl group may be any substitutable position on a carbon atom or a nitrogen atom and is not particularly limited.

[0043]

The term "unsaturated 5- to 6-membered heterocycle", as used in the present invention, means a heterocycle which contains one or more heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom and has an unsaturated bond and 5 to 6 atoms present in the ring and includes an aromatic heterocycle. Specifically "unsaturated 5- to 6-membered heterocycle" includes, for example, pyrrole, imidazole, pyrazole, pyrazoline, pyridine, pyrazine, pyrimidine, pyridazine, triazine, furan,

thiophene, oxazole and thiazole. The substituting position of the heterocyclyl group may be any substitutable position on a carbon atom or a nitrogen atom and is not particularly limited.

[0044]

The term "saturated or unsaturated 5- to 6-membered heterocycle", as used in the present invention, means a saturated or unsaturated heterocycle which contains one or more heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom and has 5 to 6 atoms present in the ring and includes an aromatic heterocycle. Specifically "saturated or unsaturated 5- to 6-membered heterocycle" includes, for example, pyrrolidine, piperidine, piperazine, pyrrole, imidazole, imidazoline, pyrazole, pyrazoline, oxazoline, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, hexamethylene-imine, furan, tetrahydrofuran, thiophene, tetrahydro-thiophene, dioxolane, oxathiolane and dioxane. The substituting position of the heterocyclyl group may be any substitutable position on a carbon atom or a nitrogen atom and is not particularly limited.

[0045]

In the present invention, the "aryl group" and the "heteroaryl group" may optionally be substituted with at least one halogen atom, C_1-C_6 alkyl or C_1-C_6 alkoxy. The number of the substituent may be one to a possibly maximum number from a chemical structural standpoint. The number of the substituent is, for example, 1 to 5, preferably 1 to 3.

[0046]

In the present invention, when the nitrogen atom present in the ring is an N-oxide, the N-oxide includes, for example, a pyridine-N-oxide, a pyrimidine N-oxide, pyridazine N-oxide and a triazine N-oxide.

[0047]

The term "C_1-C_6 alkylene group", as used in the present invention, means a straight-chain or branched-chain divalent alkylene group having 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene (including, for example, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and $-CH(CH_2CH_3)-$, butylenes (including, for example, $-CH_2CH_2CH_2CH_2-$, $-CH(-CH_3)CH_2CH_2-$, $-CH_2CH(-CH_3)CH_2-$, $-CH_2CH_2CH(-CH_3)-$, $-CH(-CH_2CH_3)CH_2-$, $-CH_2CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$ and $-CH(-CH_3)CH(-CH_3)-$.

[0048]

The term "hydroxyl C_1-C_6 alkyl group", as used in the present invention, means an alkyl group substituted with a hydroxyl group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2-hydroxyprorpyl, 1-hydroxypropyl, 2-hydroxy-prop-2-yl and 1-hydroxy-prop-2-yl.

[0049]

The term "C_1-C_6 alkoxy C_1-C_6 alkyl group", as used in the present invention, means an alkyl group substituted with an alkoxy group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and the already defined C_1-C_6

alkoxy group as an alkoxy moiety and include, for example, methoxymethyl, 2-methoxyethyl, 1-methoxyethyl, 3-methoxypropyl, 2-methoxyporpyl, 1-methoxypropyl, 2-methoxy-prop-2-yl, 1-methoxy-prop-2-yl, ethoxymethyl, 2-ethoxyethyl, 1-ethoxyethyl, 3-ethoxypropyl, 2-ethoxypropyl, 1-ethoxypropyl, 2-ethoxy-prop-2-yl and 1-ethoxy-prop-2-yl.

[0050]

The term "amino C_1-C_6 alkyl group", as used in the present invention, means an alky group substituted with an alkyl group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, aminomethtyl, 2-aminoethyl, 1-aminoethyl, 3-aminoprpyl, 1-aminoprpyl, 2-amino-pro-2-yl and 1-amino-pro-2-yl.

[0051]

The term "(C_1-C_6 alkyl)amino group", as used in the present invention, means an amino group substituted with an amino group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, methylamino, ethylamino, n-propylamino and isopropylamino.

[0052]

The term "di(C_1-C_6 alkyl)amino group", as used in the present invention means an amino group substituted with an alkyl group which has the already independently defined two C_1-C_6 alkyl groups as alkyl moieties and includes, for example, dimethylamino, ethylmethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl-n-propylamino and methyl-isopropylamino.

The term "(C_1-C_6 alkyl)amino C_1-C_6 alkyl", as used in

the present invention, means an alkyl group substituted with an alkylamino group which has the already independently defined two C_1-C_6 alkyl groups as alkyl moieties and include, for example, (methylamino)methyl, 2-(methylamino)ethyl, 1-(methylamino)ethyl, 3-(methylamino)-propyl, 2-(methylamino)propyl, 1-(methylamino)propyl, 2-(methylamino)prop-2-yl and 1-(methylamino)-prop-2-yl.

[0053]

The term "di(C_1-C_6 alkyl)amino C_1-C_6 alkyl", as used in the present invention, means an alkyl group substituted with an alkylamino group which has the already independently defined three C_1-C_6 alkyl groups as alkyl moieties and include, for example, (dimethylamino)methyl, 2-(dimethylamino)ethyl, 1-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 2-(dimethylamino)propyl, 1-(dimethylamino)propyl, 2-(dimethylamino)prop-2-yl and 1-(dimethylamino)-prop-2-yl.

[0054]

The term "amino C_1-C_6 alkylamino group", as used in the present invention, means an alkylamino group substituted with an amino group which has the already defined C_1-C_6 alkyl group as an alkyl moiety and includes, for example, (2-aminoethyl)amino, (3-aminopropyl)amino and (4-aminobutyl)amino.

[0055]

The term "mono(C_1-C_6 alkyl)amino C_1-C_6 alkylamino group", as used in the present invention, means an alkylamino group substituted with an alkylamino group which

has the already defined two C_1-C_6 alkyl group as alkyl moieties and includes, for example, (2-(methylamino)ethyl)amino, (2-(ethylamino)ethyl)amino and (3-(methylamino)propyl)amino and (3-(ethylamino)propyl)amino.

[0056]

The term "di(C_1-C_6 alkyl)amino C_1-C_6 alkylamino group", as used in the present invention, means an alkylamino group substituted with an alkylamino group which has the already defined three C_1-C_6 alkyl group as alkyl moieties and includes, for example, (2-(dimethylamino)ethyl)amino, (2-(diethylamino)ethyl)amino, (3-(dimethylamino)propyl)amino and (3-(diethylamino)propyl)amino.

[0057]

In the present invention, when Ra and Rb or Ra′ and Rb′ are bonded to the same nitrogen atom, Ra and Rb or Ra′ and Rb′ may form a saturated or unsaturated 5- to 6-membered heterocycle having at least one nitrogen. The heterocycle includes, for example, pyrrole, pyrrolidine, piperazine, pyridine, morpholine and thiomorpholine.

[0058]

In the present invention, the -N(-Ra)C(=O)ORd group may be ring-closed at the bonding position of Ra and Rd to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, oxazolin-2-one and oxazolidin-2-one.

[0059]

In the present invention, the -N(-Ra)C(=O)NRa′Rb′

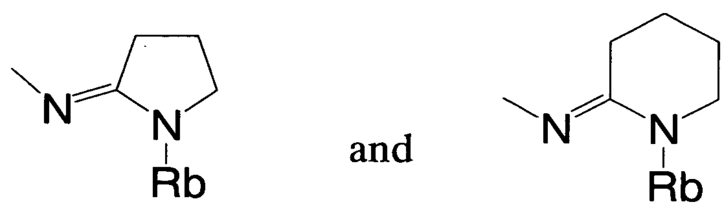
group may be ring-closed at the bonding position of Ra and Ra′ to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, imidazolin-2-one and imidazolidin-2-one.

[0060]

In the present invention, the -N=C(-Rc)NRaRb group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The -N=C(-Rc)NRaRb on forming a heterocycle includes, for example, the formulae:

[0061]

[Formula 7]



[0062]

In the present invention, the -N(-Ra)C(=O)Rc group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, pyrrolin-2-one, pyrrolidin-2-one, piperidin-2-one and morpholin-3-one.

[0063]

In the present invention, the -C(=NORa)Rc group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, isoxazole and

isoxazoline.

[0064]

In the present invention, the $-N(-Ra)SO_2Rc$ group may be ring-closed at the bonding position of Ra and Rc to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, isothiazole-1,1-dioxide and isothiazoline-1,1-dioxide.

[0065]

In the present invention, the -N[C(=O)Rc][C(=O)Rc′] group may be ring-closed at the bonding position of Rc and Rc′ to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, pyrrolidin-2,5-dione and piperidine-2,5-dione.

[0066]

In the present invention, the -C(=NORd)NRa′Rb′ group may be ring-closed at the bonding position of Rd and Ra′ to form a saturated or unsaturated 5- to 6-membered heterocycle. The heterocycle includes, for example, oxadiazoline.

[0067]

The present invention includes a salt of the compound represented by formula (1) and a pharmaceutically acceptable salt of a prodrug of the compound. These salts are produced by bringing the compound or the prodrug of the compound into contact with an acid or a base usable in the production of drugs. The salts include, for example, a hydrochloride, a hydrobromide, a hydroiodide, a sulfate, a sulfonate, a phosphate, a phosphonate; a carboxylate such

as an acetate, a citrate, a malate, a salicylate; an alkali metal such as a sodium salt and potassium salt; an alkaline earth metal salt such as a magnesium salt and a calcium salt; and an ammonium salt such as an ammonium salt, an alkylammonium salt, a dialkylammonium salt, a trialkylammonium salt and a tetraalkylammonium salt.

[0068]

The term "prodrug", as used in the present invention, means a derivative of the compound of formula (1) which is converted into the compound of formula (1) or its pharmaceutically accepatable salts by enzymatic or non-enzymatic reaction under physiological conditions. When the prodrug is administered to a patient, it ma be inactive, but in a living body, it is converted to be in the form of the compound of formula (1) which is active.

[0069]

The term "prodrug" in the present invention includes, for example, that:

(1) when the compound of the formula (1) has a hydroxyl group in the molecule, the hydroxyl group is protected with a protective group;

(2) when the compound of the formula (1) has a -NH- group or an amino group in the molecule a compound, the -NH-group or the amino group is protected with a protective group; and

(3) when the compound of the formula (1) has a carboxyl group in the molecule, the carboxyl group is converted to an ester group or an amide group which may be substituted.

[0070]

Herein, examples of the protective group for the hydroxyl group include, for example, a C_1-C_6 alkylcarbonyl group, an arylcarbonyl group, a heteroarylcarbonyl group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylaminocarbonyl group, a di(C_1-C_6 alkyl)amino-carbonyl group, an aryl C_1-C_6 alkyl group, a heteroaryl C_1-C_6 alkyl group, an aryl C_1-C_6 alkylaminocarbonyl group, $-P(=O)(OH)_2$, $-CH_2OP(=O)(OH)_2$, a C_1-C_6 alkyl group, a C_1-C_6 alkylsulfonyl group, an ((amino C_1-C_6 alkyl)carbonyloxy)C_1-C_6 alkyl group and an unsaturated heterocyclic carbonyloxy C_1-C_6 alkyl group. Further, the protected hydroxyl group may be an ester of a natural type or non-natural type amino acid, an ester of a dipeptide, an ester of a tripeptide or an ester of tetrapeptide. Preferred protective groups for the hydroxyl group include, for example, an acetyl group, a glycidyl group, a sarcosyl group, an alanyl, group, a leucyl group and a (5-methyl-2-oxo-1,3-dioxolo-4-yl)methyl group.

[0071]

Examples of the protective group for the -NH- group or amino group include, for example, a C_1-C_6 alkylcarbonyl group, an arylcarbonyl group, a heteroarylcarbonyl group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylaminocarbonyl group, a di(C_1-C_6 alkyl)aminocarbonyl group, an aryl C_1-C_6 alkyl group, a heteroaryl C_1-C_6 alkyl group, an (aryl C_1-C_6 alkyl)aminocarbonyl group, $-P(=O)(OH)_2$, $-CH_2OP(=O)(OH)_2$, a C_1-C_6 alkyl group and a C_1-C_6 alkylsulfonyl group. Further, the protected -NH- group or amino group may be an amide of

a natural type or non-natural type amino acid, an amide of a dipeptide, an amide of a tripeptide amide or an amide of a tetrapeptide. Preferred protective groups for the amino group include, for example, an acetyl group, glycidyl group, sarcosyl group, an alanyl group, a leucyl group, and a (5-methyl-2-oxo-1,3-dioxolo-4-yl)methyl group.

[0072]

Further, the amino group may form a saturated or unsaturated heterocyclyl group such as a phthalimide group, a succinimide group, a glutarimide group or a 1-pyrrolyl group by the protection.

[0073]

When the carboxyl group is converted to an ester group or an amide group which may be substituted, examples of the ester group include, for example, a C_1-C_6 alkyl ester, an aryl ester, a heteroaryl ester, an aryl C_1-C_6 alkyl ester, a heteroaryl C_1-C_6 alkyl ester, a C_1-C_6 alkoxy C_1-C_6 alkyl easter, an aryloxy C_1-C_6 alkyl ester, an aryl C_1-C_6 alkyloxy C_1-C_6 alkyl ester, a hydroxyl C_1-C_6 alkyl ester, an amino C_1-C_6 alkyl ester, a C_1-C_6 alkylamino C_1-C_6 alkyl ester and a di(C_1-C_6 alkyl)amino C_1-C_6 alkyl ester. Preferred ester groups are a methyl ester group, an ethyl ester group, 2-hydroxyethyl ester and a 2-(dimethylamino)-ethyl ester group.

[0074]

The amide group is, for example, an amide group represented by $-C(=O)NR^{21}R^{22}$, and R^{21} and R^{22} can be independently selected from a hydrogen atom, a C_1-C_6 alkyl

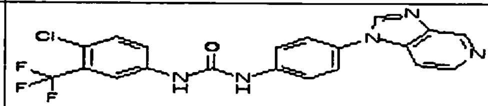
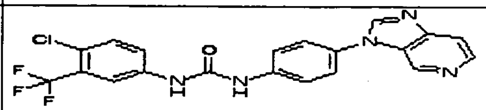
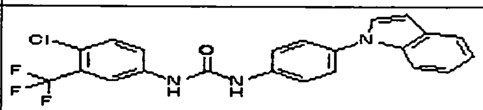
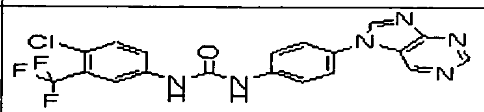
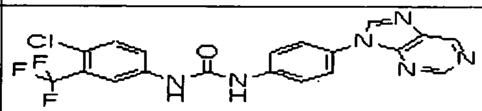
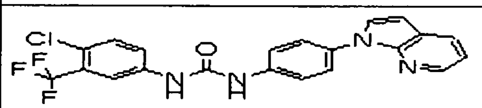
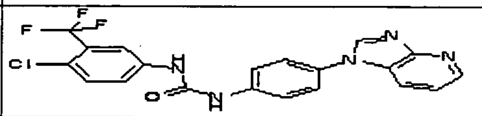
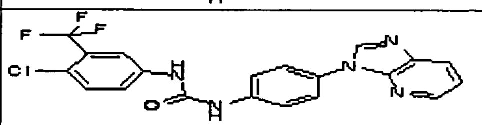
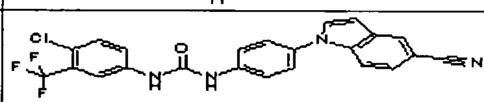
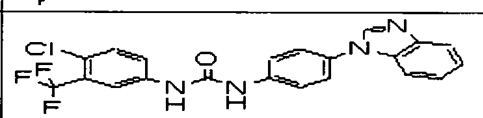
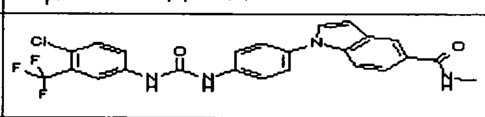
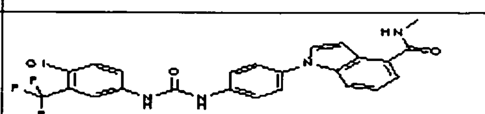
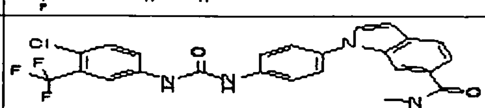
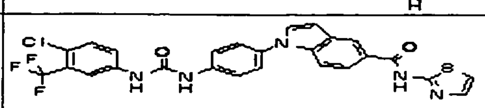
group, an aryl group, a heteroaryl group, an aryl C_1-C_6 alkyl group, a heteroaryl C_1-C_6 alkyl group, a C_1-C_6 alkoxy C_1-C_6 alkyl group, an aryloxy C_1-C_6 alkyl group, an aryl C_1-C_6 alkyloxy C_1-C_6 alkyl group, a hydroxyl C_1-C_6 alkyl group, an amino C_1-C_6 alkyl group, a C_1-C_6 alkylamino C_1-C_6 alkyl group, a di(C_1-C_6 alkyl)amino C_1-C_6 alkyl group, a hydroxyl group and an alkoxy group. R^{21} and R^{22} are preferably each a methyl group, an ethyl group, a 2-hydroxyethyl group or a 2-(dimethylamino)ethyl group.

[0075]

As more specific examples of the compound represented by formula (1) of the present invention, the compounds as described below can be exemplified but the present invention is not limited to them.

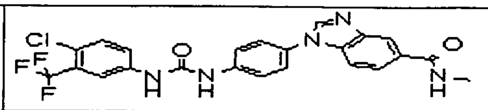
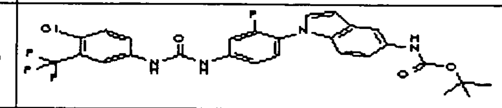
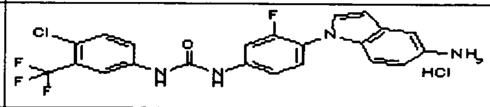
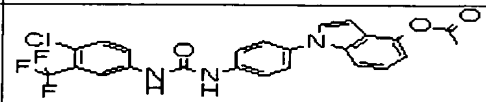
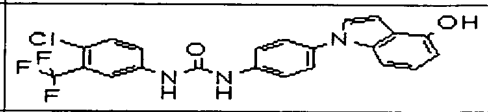
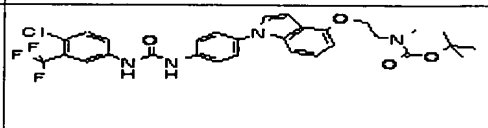
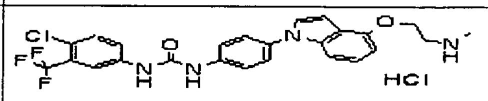
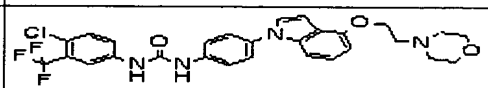
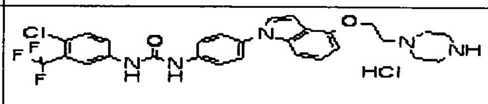
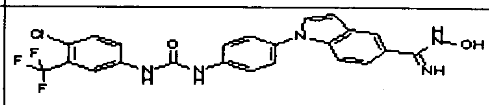
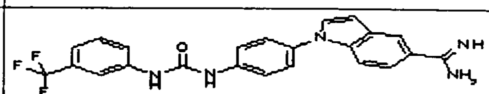
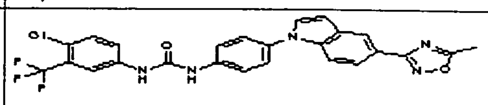
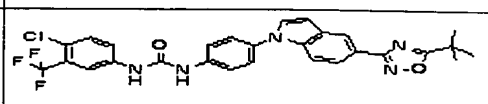
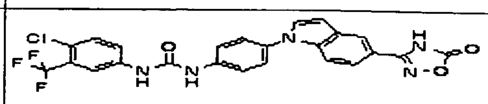
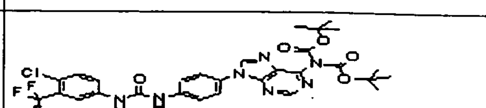
[0076]

[Table 1-1]

	Structural formula	Name of compound	Example No.
1		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-c]pyridin-1-ylphenyl)urea	Example 1
2		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-c]pyridin-3-ylphenyl)urea	Example 2
3		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-indol-1-ylphenyl)urea	Example 3
4		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-purin-7-ylphenyl urea	Example 4
5		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-purin-9-ylphenyl)urea	Example 5
6		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-pyrrolo-[2,3-b]pyridin-1-ylphenyl)urea	Example 6
7		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-b]pyridin-1-ylphenyl)urea	Example 7
8		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-b]pyridin-3-ylphenyl)urea	Example 8
9		1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cyanoindol-1-yl)phenyl]urea	Example 9
10		1-(4-Benzimidazol-1-ylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea	Example 10
11		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indole-5-carboxylic acid methylamide	Example 11
12		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indole-4-carboxylic acid methylamide	Example 12
13		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indole-6-carboxylic acid methylamide	Example 13
14		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indole-5-carboxylic acid thiazol-2-ylamide	Example 14

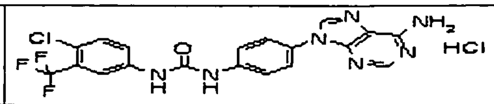
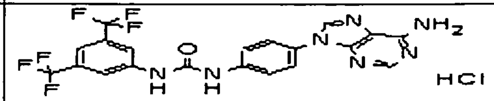
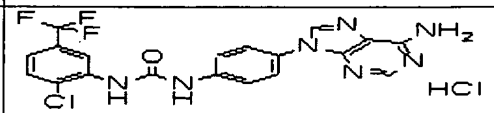
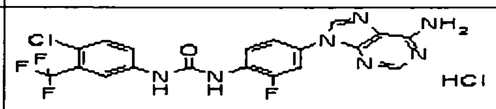
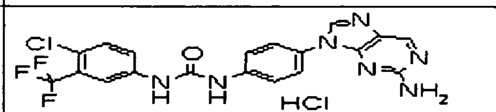
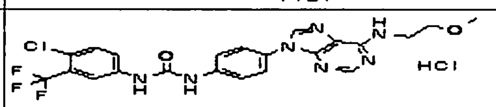
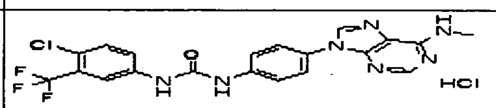
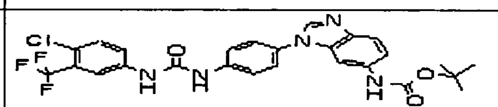
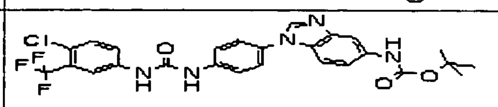
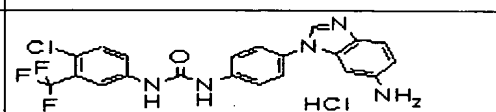
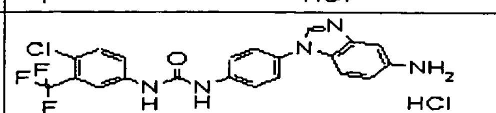
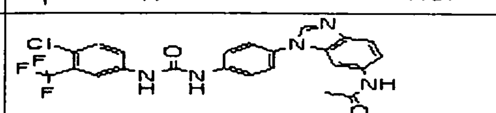
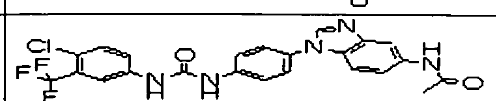
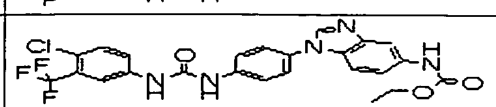
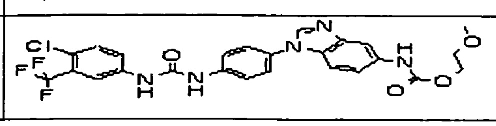
[0077]

[Table 1-2]

15		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazole-5-carboxylic acid methylamide	Example 15
16		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester	Example 16
17		1-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 17
18		Acetic acid 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indol-4-yl ester	Example 18
19		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-[4-(4-hydroxyindol-1-yl)phenyl]urea	Example 19
20		[2-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester	Example 20
21		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[4-(2-methylaminoethoxy)indol-1-yl)phenyl]urea hydrochloride	Example 21
22		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[4-(2-morpholin-4-ylethoxy)indol-1-yl]phenyl}urea	Example 22
23		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[4-(2-piperazin-1-ylethoxy)indol-1-yl]phenyl}urea hydrochloride	Example 23
24		1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine	Example 24
25		1-{4-[3-(3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-indole-5-carboxamidine	Example 25
26		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[5-(5-methyl-[1,2,4]oxadiazol-3-yl]indol-1-yl)phenyl}urea	Example 26
27		1-{4-[5-(5-tert-Butyl-[1,2,4]-oxadiazol-3-yl)indol-1-yl] phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)urea	Example 27
28		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl]-phenyl)urea	Example 28
29		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]-phenyl}urea	Example 29

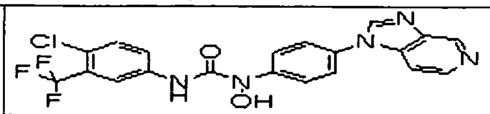
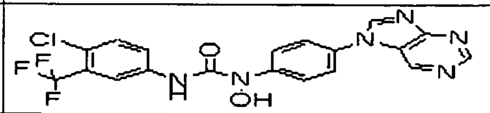
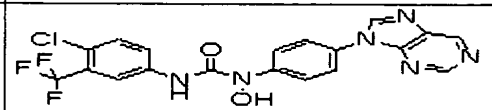
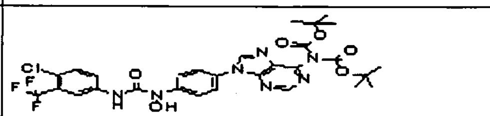
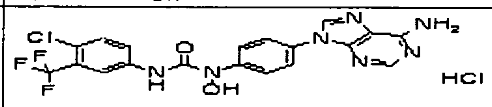
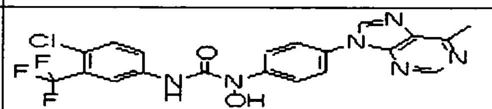
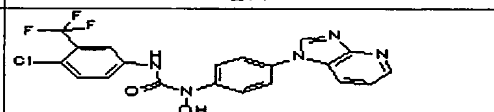
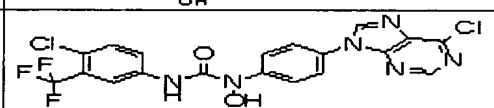
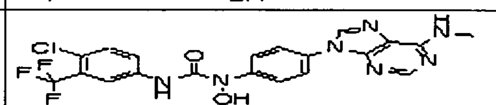
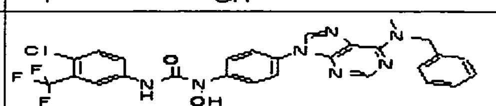
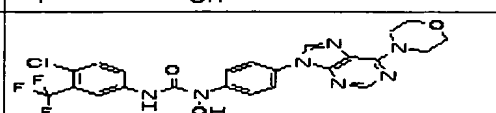
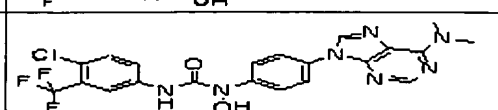
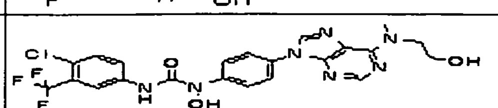
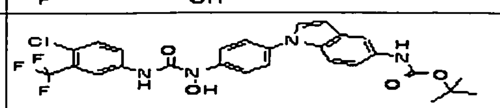
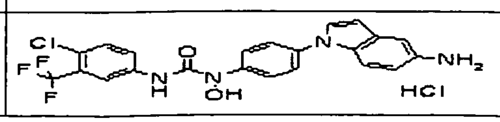
[0078]

[Table 1-3]

30		1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride	Example 30
31		1-[4-(6-Aminopurin-9-yl)phenyl]-3-(3,5-bis-(trifluoromethyl)-phenyl)urea hydrochloride	Example 31
32		1-[4-(6-Aminopurin-9-yl)phenyl]-3-(2-chloro-5-(trifluoromethyl)-phenyl)urea hydrochloride	Example 32
33		1-[4-(6-Aminopurin-9-yl)-2-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 33
34		1-[4-(2-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride	Example 34
35		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(2-methoxy-ethylamino)-purin-9-yl]phenyl}-urea hydrochloride	Example 35
36		1-(4-Chloro-3-(trifluoromethyl)-phenyl)-3-[4-(6-(methylamino)-purin-9-yl)phenyl]urea hydrochloride	Example 36
37		(3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)carbamic acid tert-butyl ester	Example 37
38		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid tert-butyl ester	Example 38
39		1-[4-(6-Aminobenzimidazol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 39
40		1-[4-(5-Aminobenzimidazol-1-yl)-phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride	Example 40
41		N-(3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)acetamide	Example 41
42		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)acetamide	Example 42
43		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid ethyl ester	Example 43
44		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid 2-methoxyethyl ester	Example 44

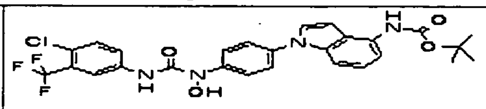
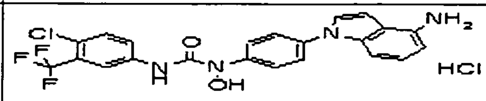
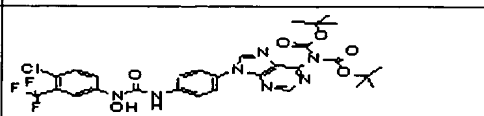
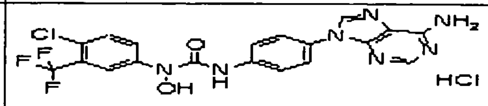
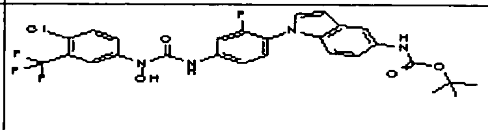
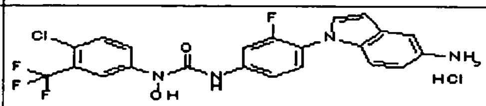
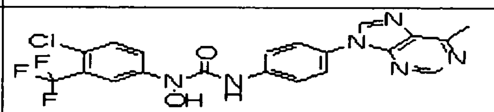
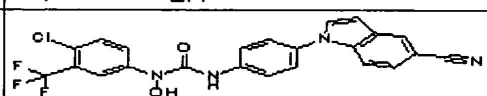
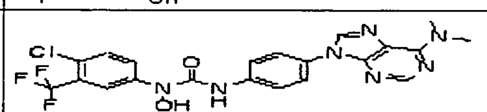
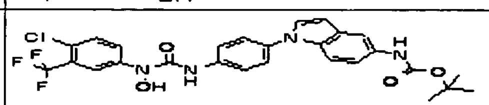
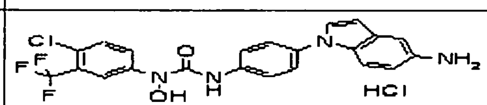
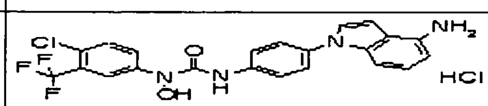
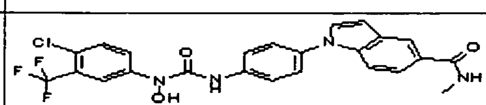
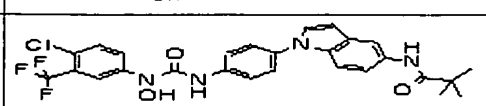
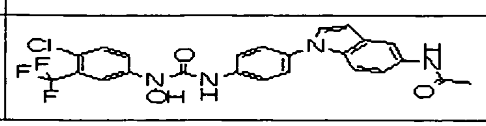
[0079]

[Table 1-4]

45		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hyrdoxy-3-(4-imidazo[4,5-c]pyridin-3-yl-phenyl)urea	Example 45
46		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hyrdoxy-3-(4-purin-7-ylphenyl)urea	Example 46
47		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hyrdoxy-3-(4-purin-9-ylphenyl)urea	Example 47
48		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-3-hydroxyurea	Example 48
49		1-[4-(6-Aminopurin-9-ylphenyl)-3-(4-chloro-3-(trifluoro-methyl)phenyl)-1-hydroxyurea hydrochloride	Example 49
50		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-hydroxy-1-[4-(6-(methylpurin-9-yl)phenyl)-urea	Example 50
51		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-hydroxy-1-(4-imidazo[4,5-b]pyridin-1-yl-phenyl)urea	Example 51
52		1-[4-(6-Chloropurin-9-yl)-phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxy-urea	Example 52
53		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-hydroxy-1-[4-(6-(methylamino)purin-9-yl)-phenyl]urea	Example 53
54		1-{4-[6-(benzyl-methylamino)-purin-9-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea	Example 54
55		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hydroxy-3-[4-(6-morpholin-4-ylpurin-9-yl)-phenyl]urea	Example 55
56		3-(4-Chloro-3-(trifluoro-methyl)phenyl)-1-[4-(6-dimethylamino-purin-9-yl)-phenyl]-1-hydroxyurea	Example 56
57		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-hydroxy-3-(4-{6-[(2-hydroxyethyl)-methyl-amino]purin-9-yl}phenyl)urea	Example 57
58		(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxy-ureido]phenyl}-1H-indol-5-yl)-carbamic acid tert-butyl ester	Example 58
59		1-4-(5-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoro-methyl)phenyl)-1-hydroxyurea hydrochloride	Example 59

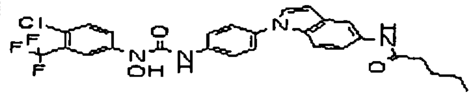
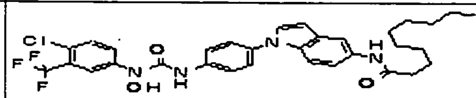
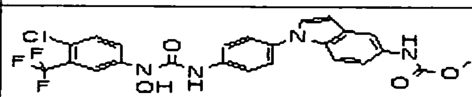
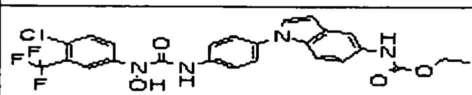
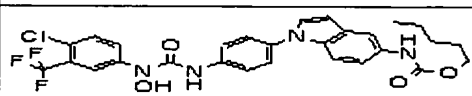
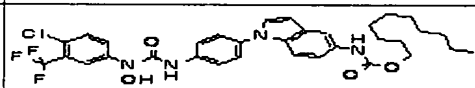
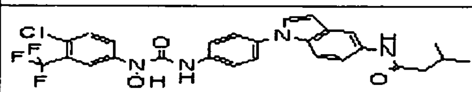
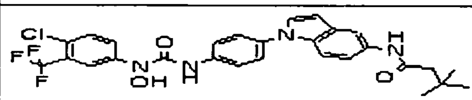
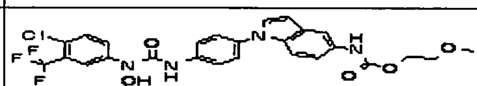
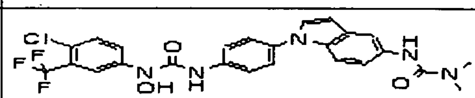
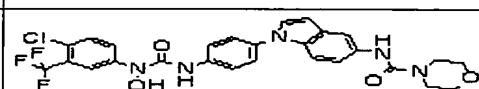
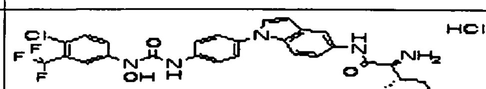
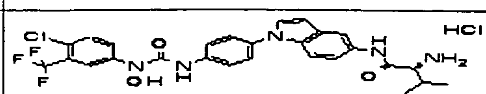
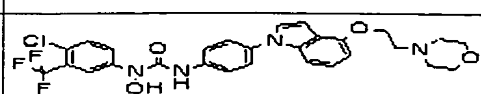
[0080]

[Table 1-5]

60		(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxy-ureido]phenyl}-1H-indol-4-yl)-carbamic acid tert-butyl ester	Example 60
61		1-[4-(4-Aminoindol-1-yl)-phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxy-urea hydrochloride	Example 61
62		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)-purin-9-yl]phenyl}-1-hydroxy-urea	Example 62
63		1-[4-(6-Aminopurin-9-yl)-phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxy-urea hydrochloride	Example 63
64		(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxy-ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester	Example 64
65		3-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-1-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea	Example 65
66		3-(4-Choloro-3-(trifluoro-methyl)phenyl)-3-hydroxy-1-[4-(6-methylpurin-9-yl)phenyl]urea	Example 66
67		1-(4-Choloro-3-(trifluoro-methyl)phenyl)-3-[4-(5-cyano-indol-1-yl)phenyl]-1-hydroxy-urea	Example 67
68		3-(4-Choloro-3-(trifluoro-methyl)phenyl)-1-[4-(6-di-methylaminopurin-9-yl)phenyl]-3-hydroxyurea	Example 68
69		(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxy-ureido]phenyl}-1H-indol-5-yl)-carbamic acid tert-butyl ester	Example 69
70		1-[4-(5-Aminoindol-1-yl)-phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxyurea hydrochloride	Example 70
71		1-[4-(4-Aminoindol-1-yl)-phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxyurea hydrochloride	Example 71
72		(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxy-ureido]phenyl}-1H-indole-5-carboxylic acid methylamide	Example 72
73		N-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxy-ureido]phenyl}-1H-indol-5-yl)-2,2-dimethylpropionamide	Example 73
74		N-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxy-ureido]phenyl}-1H-indol-5-yl)-acetamide	Example 74

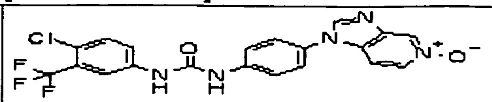
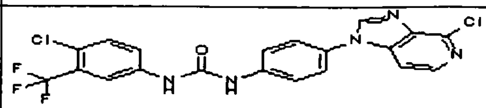
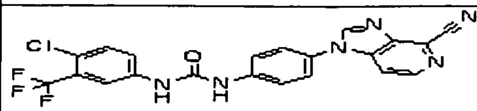
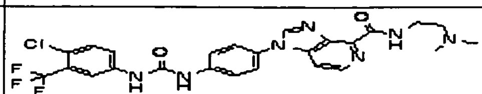
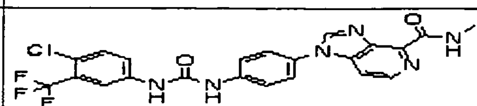
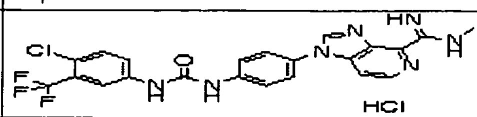
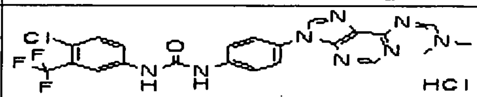
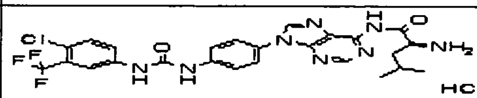
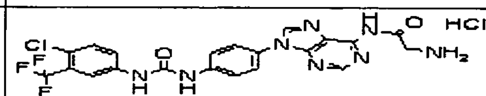
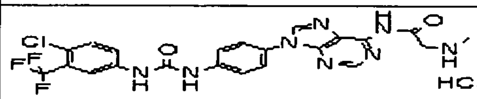
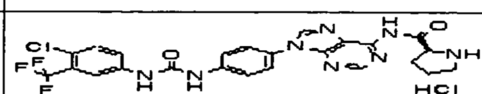
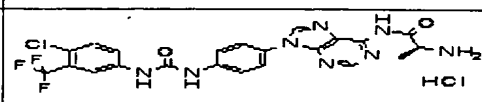
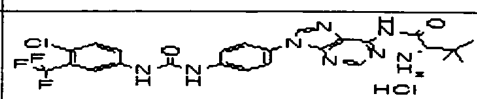
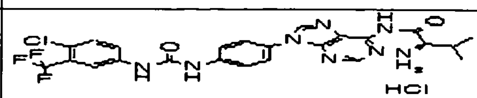
[0081]

[Table 1-6]

75		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-pentanamide	Example 75
76		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-decanamide	Example 76
77		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid methyl ester	Example 77
78		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid ethyl ester	Example 78
79		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid pentyl ester	Example 79
80		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indole-5-yl)-carbamic acid decyl ester	Example 80
81		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3-methylbutylamide	Example 81
82		N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3,3-dimethylbutylamide	Example 82
83		(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-carbamic acid 2-methoxyethyl ester	Example 83
84		3-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3,3-dimethylurea	Example 84
85		Morpholine-4-carboxylic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-amide	Example 85
86		(2S,3S)-2-Amino-3-methyl-pentanoic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)-amide	Example 86
87		(S)-2-Amino-N-(1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)-3-methylbutylamide	Example 87
88		1-(4-Choloro-3-(trifluoromethyl)phenyl)-1-hydroxy-3-{4-[4-(2-morpholin-4-yl-ethoxy)-indol-1-yl]phenylurea	Example 88

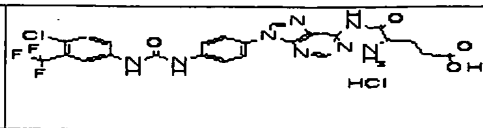
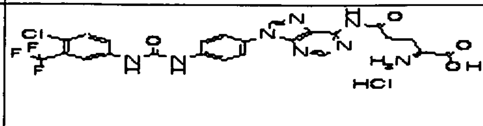
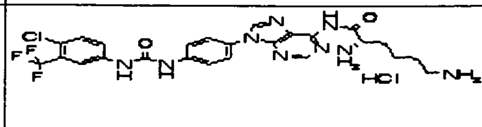
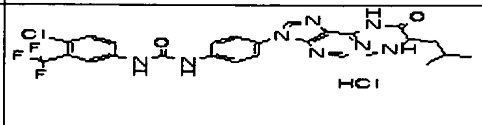
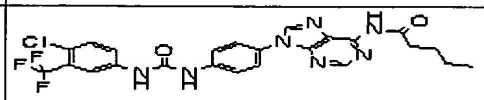
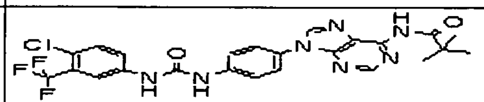
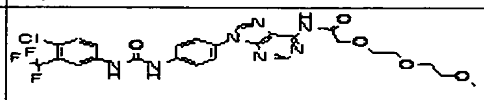
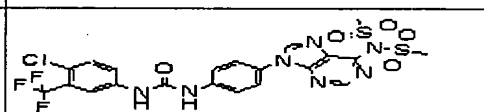
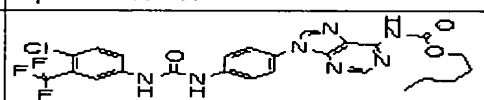
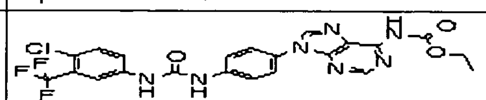
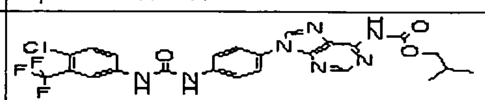
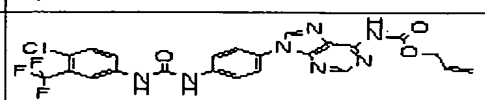
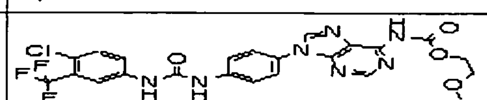
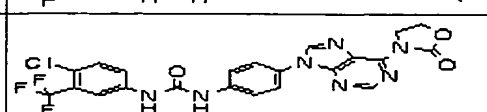
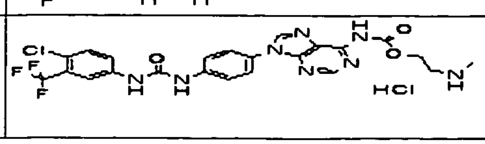
[0082]

[Table 1-7]

89		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea	Example 89
90		1-[4-(4-Chloro-imidazo[4,5-c]-pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea	Example 90
91		1-(4-Chloro-3-(trifluoromethyl) phenyl)-3-[4-(4-cyanoimidazo-[4,5-c]pyridin-1-yl)phenyl]urea	Example 91
92		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-dimethyl-aminoethyl)amide	Example 92
93		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methylamide	Example 93
94		1-{4-[3-(4-Chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxamidine hydrochloride	Example 94
95		N'-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-N,N-dimethylformamidine hydro-chloride	Example 95
96		(S)-2-Amino-4-methyl-pentanoic acid 9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride	Example 96
97		2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-acetamide hydrochloride	Example 97
98		N-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-2-methylaminoacetamide hydro-chloride	Example 98
99		(S)-2-Pyrrolidine-2-carboxylic acid 9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride	Example 99
100		(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)propionamide hydrochloride	Example 100
101		(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3,3-dimethylbutylamide hydrochloride	Example 101
102		(R)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3-methylbutylamide hydro-chloride	Example 102

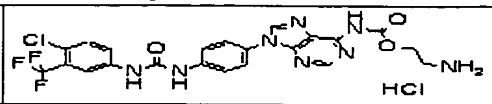
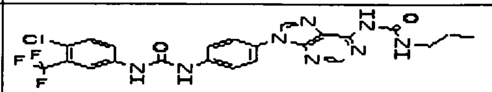
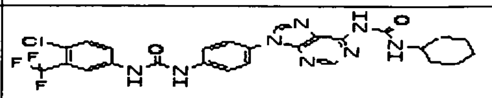
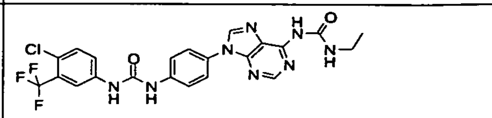
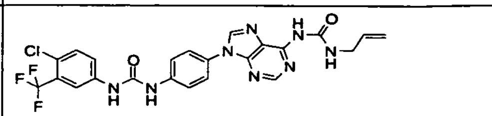
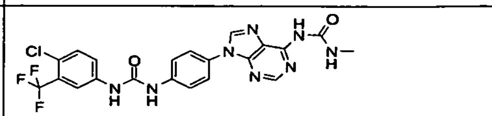
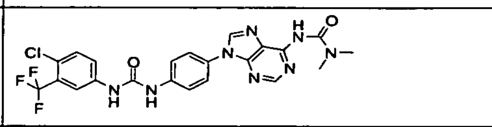
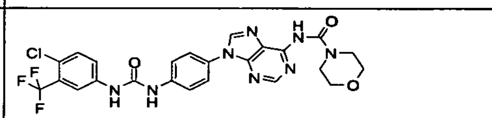
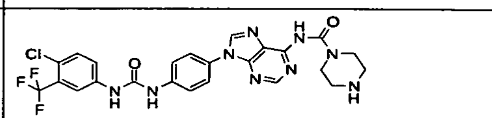
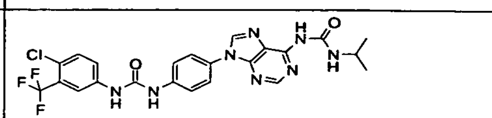
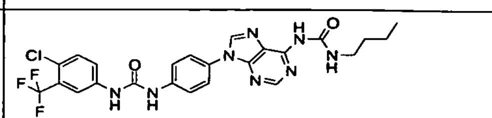
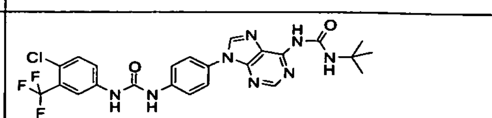
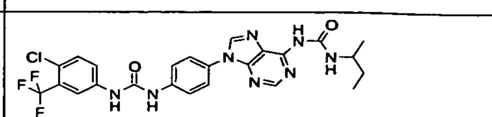
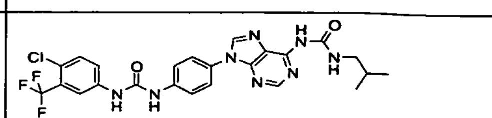
[0083]

[Table 1-8]

103		(S)-4-Amino-4-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride	Example 103
104		(S)-2-Amino-4-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride	Example 104
105		(S)-2,6-Diaminohexanoic acid (9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride	Example 105
106		(S)-4-Methyl-2-methylamino-pentanoic acid (9-{4-[3-(4-chloro-3-(tri-fluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride	Example 106
107		Pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)amide	Example 107
108		N-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-2,2-dimethylpropionamide	Example 108
109		N-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-2-[2-(2-methoxyethoxy)ethoxy]acetamide	Example 109
110		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(di-methanesulfonylamino)purin-9-yl]phenyl}urea	Example 110
111		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid pentyl ester	Example 111
112		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid ethyl ester	Example 112
113		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid isobutyl ester	Example 113
114		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid allyl ester	Example 114
115		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid 2-methoxyethyl ester	Example 115
116		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2-oxo-oxazolidin-3-yl)purin-9-yl]phenyl}urea	Example 116
117		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid 2-methylamino-ethyl ester hydrochloride	Example 117

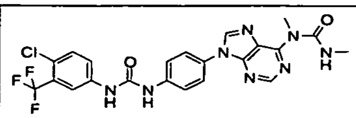
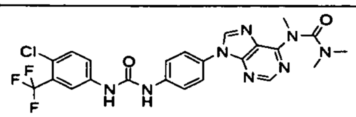
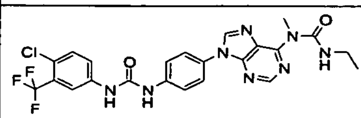
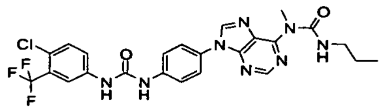
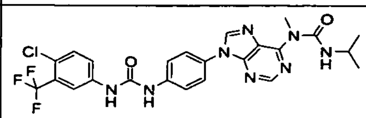
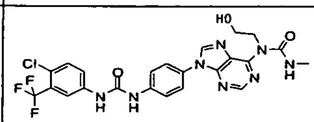
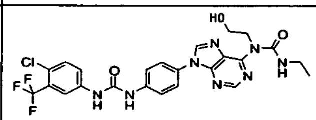
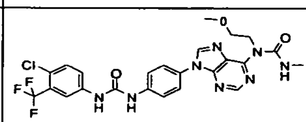
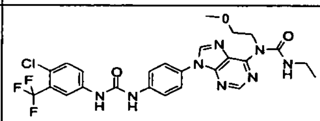
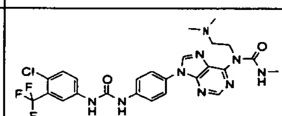
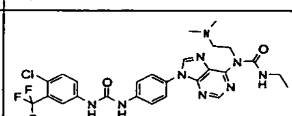
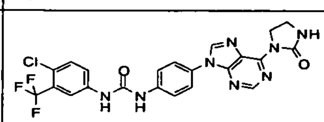
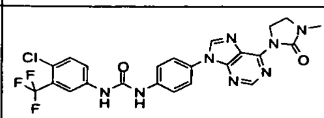
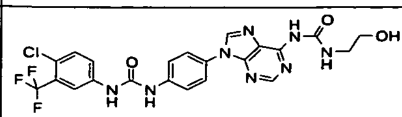
[0084]

[Table 1-9]

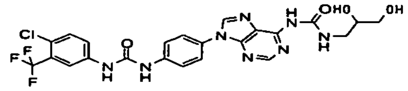
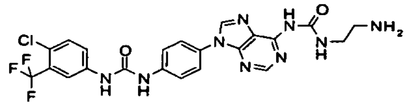
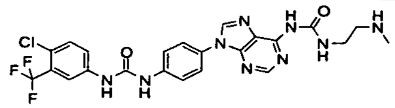
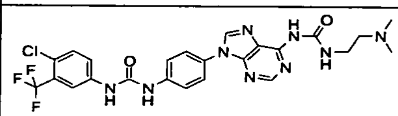
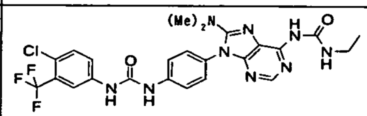
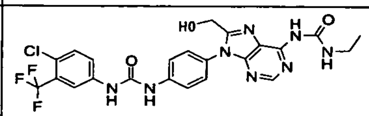
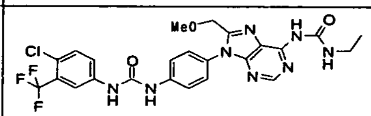
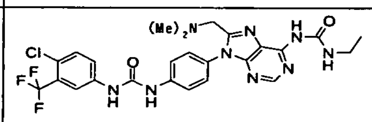
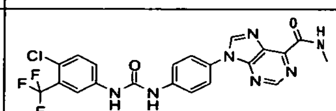
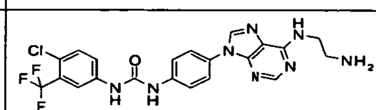
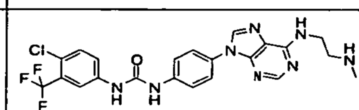
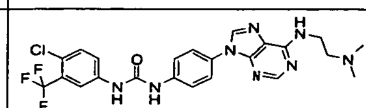
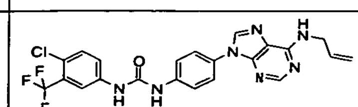
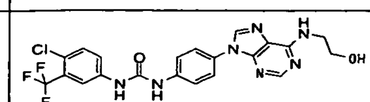
118		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)carbamic acid 2-amino-ethyl ester hydrochloride	Example 118
119		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-propylurea	Example 119
120		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-cyclohexylurea	Example 120
121		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethylurea	Example 121
122		1-Allyl-3-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-urea	Example 122
123		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-methylurea	
124		3-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1,1-dimethylurea	
125		Morpholine-4-carboxylic acid (9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide	
126		Piperidine-1-carboxylic acid (9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide	
127		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)—3-isopropylurea	
128		1-Butyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-urea	
129		1-tert-Butyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea	
130		1-sec-Butyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea	
131		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-isobutylurea	

[0085]

[Table 1-10]

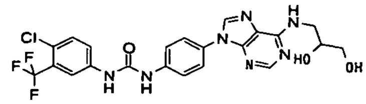
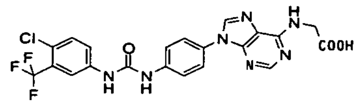
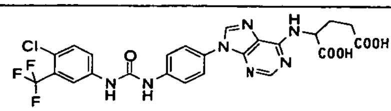
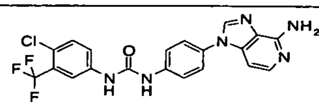
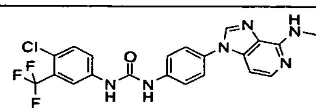
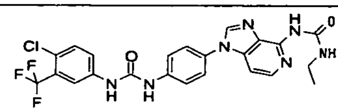
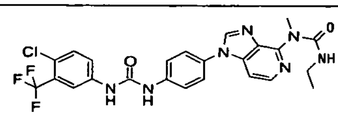
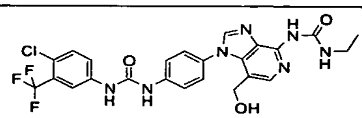
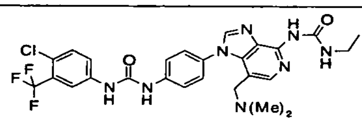
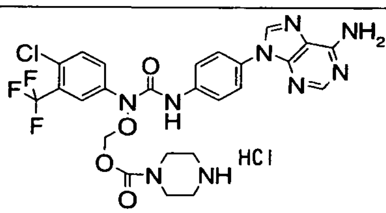
132		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1,3-dimethylurea	
133		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1,3,3-trimethylurea	
134		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethyl-1-methylurea	
135		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-methyl-3-propylurea	
136		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-isopropyl-1-methylurea	
137		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-hydroxyethyl)-3-methylurea	
138		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethyl-1-(2-hydroxyethyl)urea	
139		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-methoxyethyl)-3-methylurea	
140		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-ethyl-1-(2-methoxyethyl)urea	
141		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-dimethylaminoethyl)-3-methyl-urea	
142		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-1-(2-dimethylaminoethyl)-3-ethyl-urea	
143		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2-oxo-imdazolin-1-yl)purin-9-yl]-phenyl}urea	
144		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(3-methyl-2-oxo-imdazolin-1-yl)purin-9-yl]phenyl}urea	
145		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2-hydroxyethyl)urea	

[0086]
[Table 1-11]

146		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2,3-dihydroxypropyl)urea	
147		1-(2-Aminoethyl)-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea	
148		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2-methylaminoethyl)urea	
149		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)-3-(2-dimethylaminoethyl)urea	
150		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-8-dimethylamino-9H-purin-6-yl)-3-ethylurea	
151		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-8-hydroxymethyl-9H-purin-6-yl)-3-ethylurea	
152		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-8-methoxymethyl-9H-purin-6-yl)-3-ethylurea	
153		1-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-8-dimethylaminomethyl-9H-purin-6-yl)-3-ethylurea	
154		9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purine-6-carboxylic acid methylamide	
155		1-{4-[6-(2-Amino-ethylamino)-purin-9-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea	
156		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-(6-(2-methylamino-ethylamino)purin-9-yl)phenyl}urea	
157		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2-dimethylamino-ethylamino)-purin-9-yl]phenyl}urea	
158		1-[4-(6-Allylamino-purin-9-yl)phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)urea	
159		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2-hydroxy-ethylamino)-purin-9-yl]phenyl}urea	

[0087]

[Table 1-12]

160		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-{4-[6-(2,3-dihydroxy-propylamino)-purin-9-yl]phenyl}urea	
161		(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-ylamino)-acetic acid	
162		2-(9-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-ylamino)-pentanedicarboxylic acid	
163		1-[4-(4-Aminoimidazo[4,5-c]-pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea	
164		1-(4-Chloro-3-(trifluoro-methyl)phenyl)-3-[4-(4-methylamino-imidazo[4,5-c]-pyridin-1-yl)phenyl]urea	
165		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]-pyridin-4-yl}-3-ethylurea	
166		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]-pyridin-4-yl}-3-ethyl-1-methylurea	
167		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-7-hydroxymethyl-1H-imidazo[4,5-c]pyridin-4-yl}-3-ethyurea	
168		1-(1-{4-[3-(4-Chloro-3-(tri-fluoromethyl)phenyl)ureido]-phenyl}-7-dimethylamino-methyl-1H-imidazo[4,5-c]- pyridin-4-yl)-3-ethylurea	
169		3-[4-[6-Aminopurin-9-yl]-phenyl]-1-(4-chloro-3-(tri-fluoromethylphenyl)11-(1-piperazinecarbonyloxy-methoxy)urea hydrochloride	

[0088]

The method for preparing the compound of the present invention will now be explained. Further, when the defined groups undergo an undesirable chemical conversion under the

conditions for carrying out the method in the preparation method as shown below, for example, by using means to protect and deprotect the functional groups, the preparation can be performed. Herein, as the selection of a protective group and the operation of deprotection, for example, the method as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (Second Edition, John Wiley & Sons, 1991)" can be mentioned, and this may be suitably used in accordance with reaction conditions. Further, if necessary or required, the order of the reaction step for introducing a substituent and the like may be changed. As the method for preparing the compound represented by formula (1), various methods can be thought and the compound can be synthesized by using the conventional organic synthesis means and, for example, the compound can be prepared by the following method as a representative method.

[0089]

Representative Preparation Method

Preparation Method 1

The compounds which are represented by formula (1) of the present invention can be prepared, for example, according to the following method but the method for preparing the compounds of the present invention is not limited thereto. The compounds of the present inventions are all novel compounds not described in literature but can be prepared by using known chemical techniques. Further, as the raw material compounds which are used in the

preparation, commercially available compounds may be used or the raw material may be prepared according to the conventional method, if necessary. Further, in Reaction Steps 1 to 4 and their explanation, R^1 to R^7, Q, Z^1, Z^2, W, Ra, Rb, Ra', Rb', Rc, Rc', Rd and Rd' mean the same as in defined in the above described formula (1). Further, L is an elimination group such as a halogen atom, a methane-sulfonyloxy group and a p-toluenesulfonyloxy group, and PG is a protective group such as a C_1-C_6 alkylcarbonyl group including an acetyl group, a C_1-C_6 alkoxycarbonyl group including t-butoxycarbonyl group, an aryl C_1-C_6 alkyl-carbonyl group including a benzyloxycarbonyl group and tri(C_1-C_6 alkyl)silyl group including t-butylmethylsilyl group.

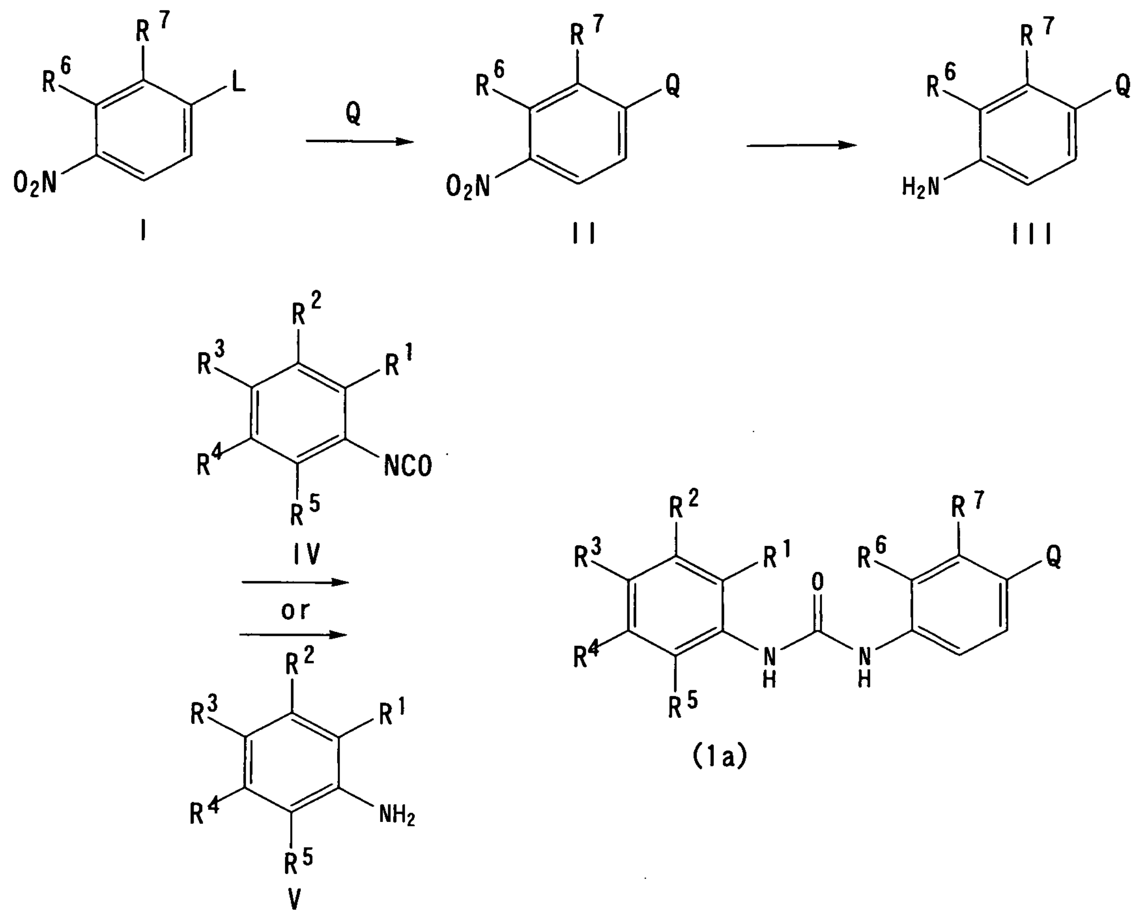
[0090]

1. General Method for Synthesizing Compound (1a) When Z^1 and Z^2 are Both H

Reaction Step 1

[0091]

[Formula 8]



[0092]

A 4-heteroaryl nitrobenzene derivative (II) can be prepared by the method as described in the known document [Ichikawa, J. et al., J. Org. Chem., Vol.61(8), 2763-2769, 1996] or a similar method. According to this method, a nitrobenzene derivative (I) can is allowed to react with a heteroaryl derivative Q in the presence of a suitable base (for example, sodium hydride, potassium carbonate or potassium butoxide) in a suitable solvent [for example, DMF (dimethylformamide) or DMSO (dimethyl sulfoxide)] to obtain a 4-heteroarylnitrobenzene derivative (II). The obtained

4-heteroarylnitrobenzene (II) is isolated and purified and then is reduced to a 4-heteroarylaniline derivative (III) by a known method (for example, catalytic reduction). By allowing the obtained 4-heteroarylaniline derivative (III) to react with an aryl isocyanate derivative (IV) in a suitable solvent (for example, dichloromethane or THF), a compound represented by formula (1a) can be obtained. The aryl isocyanate derivative (IV) is easily available by utilizing a commercially available reagent or by using the method as described in the known document [Knolker, H.J. et al., Angew. Chem. Int., Ed, Engl., Vol.34(22), 2497-2500, 1995] or a similar method. The compound (1a) can be prepared by using the method as described in the known documents [Nicolaou, K.C. et al., J. Am. Chem. Soc., Vol.122(12), 2966-2967, 2000; Macor, J.E. et al., Tetrahydron Lett., Vol.40(14), 2733-2736, 1999; and Kitterigham, J. et al., Synth. Commun., Vol.30 (11), 1937-1943, 2000] or a similar method. That is, the compound represented by formula (1a) can be obtained by allowing the 4-heteroarylaniline derivative (III) to react with an aniline derivative (V) in a suitable solvent [for example, dichloromethane, THF (tetrahydrofuran) or the like] in the presence of a urea bonding-forming reagent (for example, carbonyldiimidazole, phosgene, diphosgene, triphosgene or p-nitrophenyl chloroformate) and a base [for example, pyridine, trimethylamine or a Hunig's base (N,N-diisopropylethylamine)]

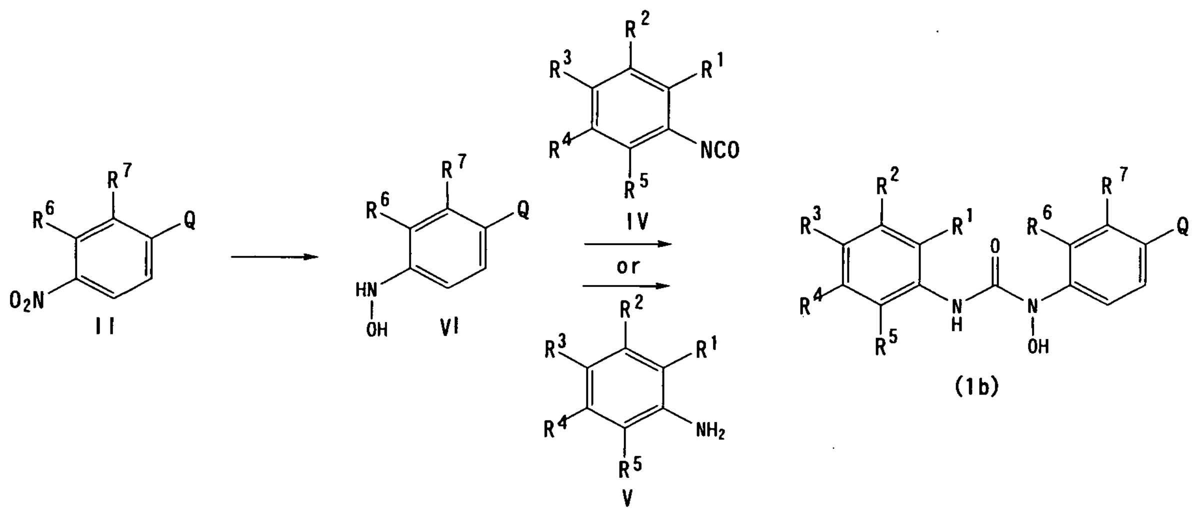
[0093]

2. General Method for Synthesizing Compound (1b) When Z^1 is H and Z^2 is OH

Reaction Step 2

[0094]

[Formula 9]



[0095]

In reaction step 2, the 4-heteroarylnitrobenzene derivative (II) obtained in Reaction Step 1 is isolated, purified and then is reduced to a 4-heteroarylphenylhydroxylamine derivative (VI) by using the known method as described in the known document (Panetta, C.A. et al., J. Org. Chem., Vol.34, 2773, 1969) or a similar method. By allowing the obtained 4-heteroarylphenylhydroxylamine derivative (VI) to react with the aryl isocyanate derivative (IV) in the same manner as in Reaction Step 1, a compound represented by formula (1b) can be obtained. Further, the compound represented by formula (1b) can be also prepared from the 4-heteroarylphenylhydroxylamine derivative (VI) and the aniline derivative (V) by using the

known method as described in the known documents [Nicolaou, K.C. et al., J. Am. Chem. Soc., Vol.122(12), 2966-2967, 2000; Macor, J. E. et al., Tetrahydron Lett., Vol.40(14), 2733-2736, 1999; and Kitterigham, J. et al., Synth. Commun., Vol.30(11), 1937-1943, 2000] or a similar method.

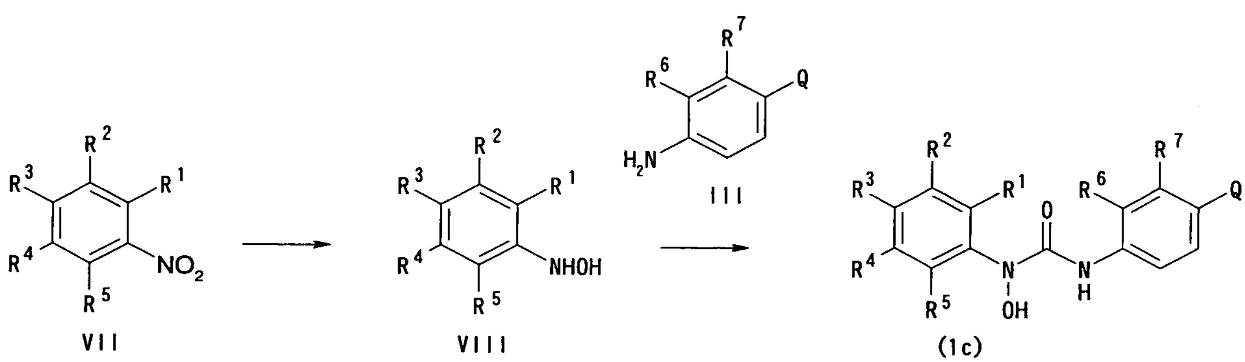
[0096]

3. General Method for Synthesizing Compound (1c) When Z^1 is OH and Z^2 is H

Reaction Step 3

[0097]

[Formula 10]



[0098]

A nitrobenzene derivative (VII) can be easily obtained by utilizing a commercially available reagent or by using the known method (for example, aromatic nitration reaction). The nitrobenzene derivative (VII) is reduced to a phenylhydroxylamine derivative (VIII) in the same manner as in Reaction Step 2. By allowing the obtained phenylhydroxylamine derivative (VIII) to react with the 4-heteroarylaniline derivative (III) obtained in Reaction Process 1 in the same manner as in reaction Step 2, a

compound represented by formula (1c) can be prepared.

[0099]

4. Functional Group Conversion of Substituent W on Heteroaryl Group Q

The compounds (1a) to (1c) in the Reaction Steps 1 to 3 can be further derivatized by the functional group conversion of a functional group W on the heteroaryl group with the use of known techniques of organic chemistry. By converting the same functional group in the starting material Q and in the stage (II) of an intermediate) in the Reaction Steps and then further performing the Reaction Steps 1 to 3, a derivative can also be obtained. On conversion of a functional group, if necessary, techniques of protection or deprotection with a suitable protective group (for example, acetyl, t-butoxy-carbonyl, benzyloxycarbonyl or t-butyldimethylsilyl) by the known method can be used.

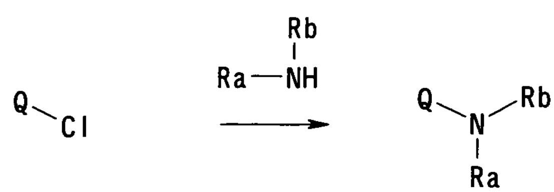
[0100]

As the representative example of functional group conversion used in the present invention, Reaction Processes 4-1 to 4-7 are given in a generalized form.

Reaction Step 4-1

[0101]

[Formula 11]



[0102]

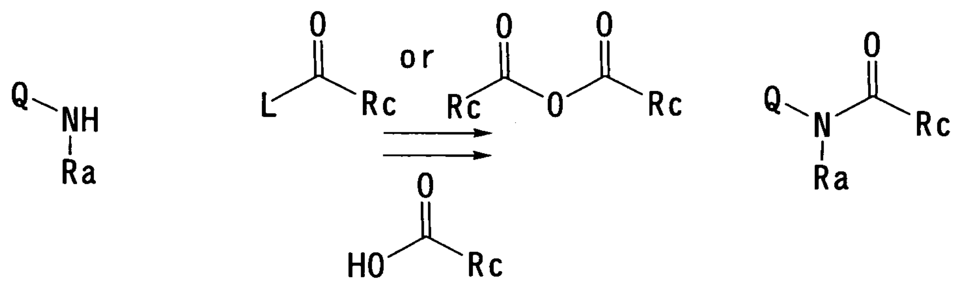
Reaction Step 4-1 is a reaction step of converting a chlorine on a heteroaryl group into an amino group. A target compound can be obtained by allowing a chloro-substituted heteroaryl compound to react with ammonia, a primary amine or a secondary amine in the absence of a solvent or in a suitable solvent (for example, methanol, ethanol or isopropanol).

[0103]

Reaction Step 4-2

[0104]

[Formula 12]



[0105]

Reaction Step 4-2 is a step of acylating an amino group on the heteroaryl group to obtain an amide derivative. A target compound can be obtained by reacting the amino substituted heteroaryl compound to react with a carboxylic acid halide or a carboxylic anhydride in the presence of a suitable base, for example, Hunig's base [N,N-diisopropylethylamine], triethylamine, pyridine or DMAP (dimethylaminopyridine)]. The target compound can be also prepared by allowing the amino substituted heteroaryl compound to react with a carboxylic acid together with a

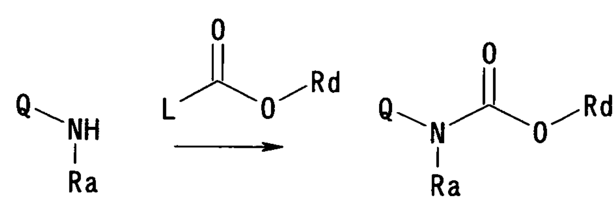
dehydration condensation agent and an auxiliary. As the dehydration condensation agent, HATU [(O-(7-azabenzo-triazol-1-yl)-N,N,N,N-tetra-methyluronium hexafluoro-phosphate), EEDQ (2-ethoxy-1-ethyoxycarbonyl-1,2-dihyroquinoline), PyBOP [(benzotriazolyloxytripyrroli-dino-phosphonium=hexafluorophosphate], PyBrOP [(bromotris-(pyrrolidino)-phosphonium=hexafluorophosphate], DDC (dicyclohexylcarbo-diimide), EDC (1-ethyl-3-(3,3'-dimethylaminopropylcarbodiimide) and the like can be mentioned. As the auxiliary, HOSu ((N-hydroxysuccinimide), HOAt (1-hydroxy-7-azabenzo-triazole), HOBt (1-hydroxy-benzotriazole) can be mentioned. As the base, trieethylamine, Hunig's base (N,N-diisopropylethylamine) or the like can be added.

[0106]

Reaction Step 4-3

[0107]

[Formula 13]



[0108]

Reaction Step 4-3 is a step of obtaining a carbamate derivative by oxycarbonylating an amino group on the heteroaryl group. A target compound can be obtained by allowing the amino substituted heteroaryl compound to react with an alkyl chloroformate in the presence of a suitable

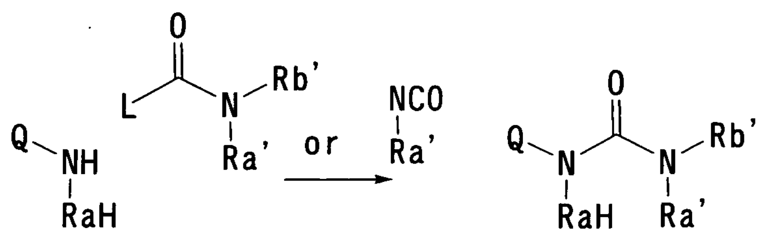
base [for example, Hunig's base (N,N-diisopropylethylamine), triethylamine, pyridine or DMAP (dimethylaminopyridine) or the like].

[0109]

Reaction Step 4-4

[0110]

[Formula 14]



[0111]

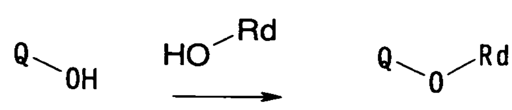
Reaction Step 4-4 is a step of obtaining a urea derivative by carbamoylating an amino group on the heteroaryl group. A target compound can be obtained by allowing the amino substituted heteroaryl compound to react with an carbamoyl chloride or an isocyanate in the presence of a suitable base [for example, Hunig's base (N,N-diisopropylethylamine), triethylamine, pyridine or DMAP (dimethylaminopyridine) or the like].

[0112]

Reaction Step 4-5

[0113]

[Formula 15]



[0114]

Reaction Step 4-5 is a step of obtaining an alkoxy

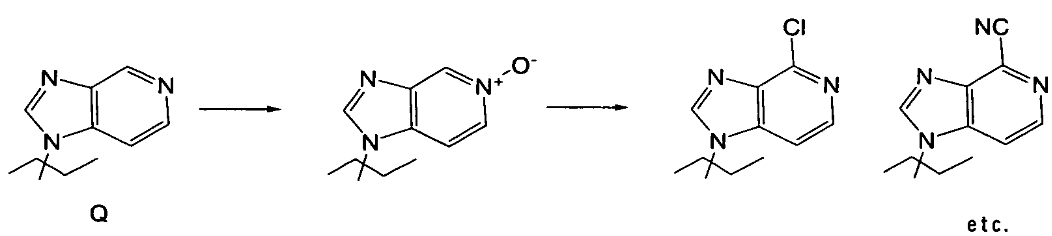
derivative by alkylating a hydroxyl group on the heteroaryl group. A target compound can be obtained byperforming the known Mitsunobu Reaction with the use of a heteroaryl compound substituted with a hydroxyl group and an alcohol corresponding to the hydroxyl group, that is, in any combination of a suitable phosphorus compound (for example, triphenylphosphine or tri-n-butylphosphine) with a suitable azo compound [for example, DEAD (diethyl azodicarboxylate) or TMAD (1,1'-azibis(N,N-dimethyl-formamide))].

[0115]

<u>Reaction Step 4-6</u>

[0116]

[Formula 16]



[0117]

The reaction Step 4-6 is a step of introducing a chlorine atom, a cyano group or the like as a substituent W when the heteroaryl group Q is imidazo[4,5-c]pyridine. Imidazo[4,5-c] pyridine can be oxidized to imidazo[4,5-c] pyridine 5-oxide in a suitable acid solvent (for example, acetic acid) with the use of an suitable oxidizing agent (for example, hydrogen peroxide) in accordance with the method described in the known document (Mizuno, Y. et al., Chem. Pharm. Bull., Vol.12(8), 866-873, 1964) or a similar method. A nucleophile such as a chlorine atom, a cyano

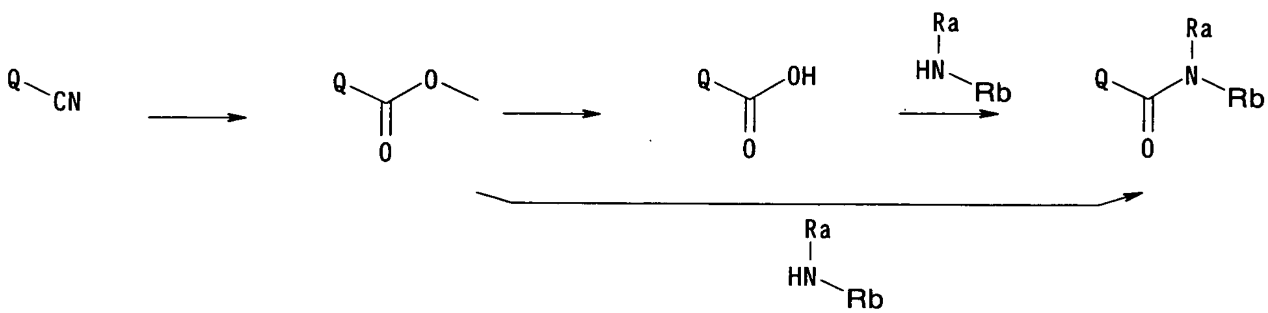
group or the like can be introduced into the imidazo[4,5-c]pyridine 5-oxide by using Reissert method or analogous methods described in the document (Hamana et al., Yakugaku Zasshi, Vol.120(2), 206-223, 2000) or a similar method.

[0118]

Reaction Step 4-7

[0119]

[Formula 17]



[0120]

Reaction Step 4-7 is a step of converting a cyano group on the heteroaryl group into a carboxamide through a carboxylate. By treating the cyano substituted heteroaryl compound in a suitable solvent (for example, methanol) with a suitable base (for example, sodium methylate) or an acid (for example, methanol hydrochloric acid), the cyano group can be converted to carboxylic acid methyl ester. By leading the carboxylic acid methyl ester to a carboxylic acid by hydrolysis and then allowing the carboxylic acid to react with the corresponding amine together with the dehydration condensation agent and the auxiliary as described in Reaction Step 4-2, the carboxamide can be prepared. The carboxamide derivative can be obtained in one

step by the exchange reaction of the carboxylic acid methyl ester derivative with the corresponding amine in a suitable solvent (for example, methanol).

[0121]

Synthesis of Raw Materials

Part of the raw materials of the compounds of the present invention are novel compounds and these compounds can be easily synthesized in the same manner as in synthesizing known raw materials or using known methods for a person with ordinary skill in the art.

[0122]

One example of the method for preparing the compounds of formula (1) relating to the present invention is shown above but the isolation/purification of the target compounds as shown in the above described Reaction Steps can be performed by applying normal chemical operations such as extraction, concentration, distillation, crystallization, filtration, recrystallization and various types of chromatographies.

[0123]

The compounds and their pharmaceutically acceptable salts of the present invention include all stereoisomers [for example, enantiomers and diastereomers (including cis- and trans-geometrical isomers)] of the compounds represented by formula (1), racemic bodies of the above described isomers and other mixtures of the above described isomers.

[0124]

Further, the compounds and their pharmaceutically acceptable salts of the present invention can exist in several tautomeric forms, for example, enol and imine forms, keto and enamine forms and their mixtures. The tautomers exist as a mixture of a tautomeric set in a solution, and one of the tautomers normally prevails in the form of a solid. The compounds of the present invention include all tautomers.

[0125]

When the compounds relating to the present invention are obtained in free-forms, they can be converted to salts hydrates or solvates which the compounds are allowed to form according to the conventional methods.

[0126]

Further, when the compounds relating to the present invention are obtained as the salts, hydrates or solvates of the compounds, they can be converted to the free forms of the compounds according to the conventional methods.

The compounds or their pharmaceutically acceptable salts relating to the present invention have excellent Ras inhibition and angiogenesis inhibition actions and excel in the internal stability and the solubility in water, and are useful as preventive or therapeutic agents (especially therapeutic agents) for the disease selected from cancer, psoriasis, atherosclerosis, chronic rheumatoid arthritis and diabetes. Furthermore, the compounds of the present invention are useful as preventive or therapeutic agents (especially therapeutic agents) for the metastasis/

infiltration of a solid cancer.

[0127]

These methods include a step of administering a pharmaceutically effective amount of a pharmaceutical composition containing the compound or its pharmaceutically acceptable salt disclosed in the present invention to a patient who requires such a treatment or has such a disease or in such a state.

[0128]

When the pharmaceutical composition of the present invention is used as a therapeutic agent or a preventive for a disease selected from cancer, psoriasis, athero-sclerosis, chronic rheumatoid arthritis and diabetes, as the administration method, oral, rectal, parenteral (intravenous, intramuscular and subcutaneous), intracisternal, vaginal, intraabdominal, intravesical and topical (a drip, a powder, an ointment, a gel or a cream) administrations, inhalation (an oral cavity or nasal spray) and the like can be mentioned. As the administration form, for example, tablets, capsules, granules, powders, pills, aqueous or nonaqueous oral solutions or suspensions and parenteral solutions filled in containers suitable for subdivision into an each dose can be mentioned. Further, the administration form can be adjusted to various administration method including a releasably adjusted formulation such as subcutaneous implantation.

[0129]

The above described pharmaceutical preparations can

be prepared by the known method with the use of additives such as an excipient, a lubricant (a coating material), a binder, a disintegrator, a stabilizer, a corrective and a diluent.

As the excipient, for example, starch such as starch, potato starch and corn starch, lactose, crystalline cellulose, calcium hydrogenphosphate and the like can be mentioned.

[0130]

As the coating material, for example, ethyl cellulose, hyroxypropyl cellulose, hydroxypropylmethyl cellulose, shellac, talc, carnauba wax, paraffin and the like can be mentioned.

[0131]

As the binder, for example, polyvinylpyrrolidone, macrogol and the same compounds as the excipients can be mentioned.

As the disintegrator, for example, the same compounds as the excipients and chemically modified starch/ celluloses such as cross calmellose sodium, carboxymethyl starch sodium and crosslinked polyvinylpyrrolidone can be mentioned.

[0132]

As the stabilizer, for example, p-hydoxybenzoic acid esters such as methylparaben and propylparaben; alchohols such chlorobutanol, benzyl alcohol and phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid.

[0133]

As the corrective, for example, a sweet taste, an acid taste, a flavor and the like which are conventionally used can be mentioned.

Further, as a solvent for preparing a liquid and a solution, for example, ethanol, phenol, chlorocresol, purified water, distilled water and the like can be used.

[0134]

As the surface active agent or an emulsifier, for example, polysorbate 80, polyoxyl 40 stearate, lauromacgol and the like can be mentioned.

When the pharmaceutical composition of the present invention is used as a therapeutic or preventive agent for a disease selected from cancer, psoriasis, athero-sclerosis, chronic rheumatoid arthritis and diabetes, the amount of use of the compound or its pharmaceutically acceptable salt of the present invention varies depending on the state of a disease, age, body weight, relative state of health, the presence or absence of other medications, the method of administration and the like. For example, for a patient (a warm-blooded animal, particularly a human), a typical daily effective dose as an active ingredient (the compound represented by formula (1) of the present invention) for an oral medicine is preferably 0.1 to 1,000 mg/kg of body weight, more preferably 0.1 to 400 mg/kg of body weight. The daily dose for the normal weight of an adult patient is preferably in the range of 10 to 800 mg. For an parenteral medicine, the daily dose is preferably 0.1 to 1,000 mg/kg

of body weight, more preferably 10 to 800 mg/kg of body weight. It is preferred that these doses are administered at one time a day or in divisions at several times in according to the state of the disease.

[Effect of The Invention]

[0135]

According to the present invention, a preventive or a therapeutic agent (particularly a therapeutic agent) which not only has the existing Raf inhibition and angiogenesis inhibition actions but also excels in the solubility in water to show highly stable oral bioavailability and excels in the safety for proliferative diseases is provided. Further, according to the present invention, a compound useful for therapeutic and preventive agent effective for proliferative diseases such as cancer and cancerous metastasis, its production method, an intermediate useful for its production, and furthermore a pharmaceutical composition comprising these compounds are provided.

[Examples]

[0136]

The present invention will be explained in more detail by examples but the present invention is not limited to these examples.

Further, the NMR analysis was performed by using JEOL JNM-EX 270 (270 MHz) or JNM GSX 400 (400 MHz), and the NMR data were shown by ppm (parts per million: δ) and the deuterium lock signal for a sample solvent was referred to. The mass spectral data were obtained by using JEOL JMS-DX

300 or JMS-SX/SX 102 or with the use of Finnigan micromass Navigator equipped with Agilent Technologies Agilent 100 gradient HPLC. The specific rotation was measured with the use of sodium D-line at room temperature.

[0137]

In the organic synthesis reactions, commercially available reagents were used without further purification. The term "room temperature" refers to a range of about 20 to 25°C. All water prohibitive reactions were performed with the use of a rotary evaporator unless expressly stated.

[0138]

In preparing the compounds, if necessary, a functional group was protected with a protective group and after preparation of the protected target compound, the protective group was removed. The selection of protective groups and the operation of deprotection were performed, for example, according to the method described in Greene and Wuts, "Protective Groups in Organic Synthesis" (Second Edition, John Wiley & Sons, 1991)".

[Example 1]

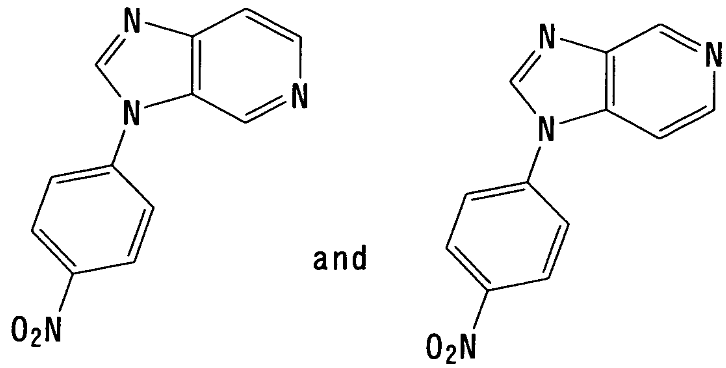
Synthesis of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 1)

Step A

Preparation of 3-(4-nitorphenyl)-3H-imidazo[4,5-c]-pyridineand 1-(4-nitrophenyl)1H-imidazo[4,5-c]pyridine

[0139]

[Formula 18]



[0140]

In 3 mL of dimethylformamide, 119 mg (1.00 mmol) of imidazo[4,5-c]pyridine was dissolved, and 138 mg (1.00 mmol) of potassium carbonate and 141 mg (1.00 mmol) of 4-fluoronitrobenzene were added thereto and the mixture solution was stirred at 80°C for two hours. The solution was diluted with 10 mL of water, and the formed precipitate was collected by filtration, washed with water, and vacuum dried. The obtained crude product was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol= 15:1) to obtain 18.9 mg (8%) of 3-(4-nitrophenyl)-3H-imidazo[4,5-c]pyridine and 66.6 mg (28%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine as yellow solids, respectively.

[0141]

3-(4-Nitrophenyl)-3H-imidazo[4,5-c]pyridine

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 7.77(2H,d,J=9.9 Hz), 7.82(1H,dd,J=1.0, 5.6 Hz), 8.30(1H,s), 8.51(2H,d,J=9.9 Hz), 8.59(1H,dd,J=1.0, 5.6 Hz), 9.03(1H,s)

1-(4-Nitrophenyl)-1H-imidazo[4,5-c]pyridine

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 7.51(1H,dd,J=1.0, 5.6

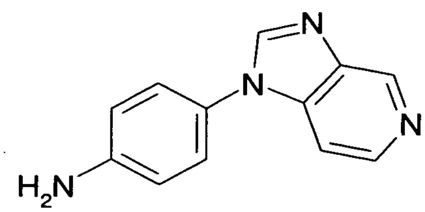
Hz), 7.72(2H,d,J=9.9 Hz), 8.23(1H,s), 8.50(2H,d,J=9.9 Hz), 8.59(1H,dd,J=1.0, 5.6 HZ), 9.24(1H,s)

Step B

Preparation of 4-(imidazo[4,5-c]pyridin-1-yl)aniline

[0142]

[Formula 19]



[0143]

In 20 mL of methanol, 33 mg (0.1237 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine prepared in Step A was dissolved and the solution was stirred on 5 mg of 10% palladium carbon in a hydrogen atmosphere at room temperature at normal pressures for one hour. After removal of the palladium carbon by filtration, the solvent was distilled under reduced pressure, and the obtained product was vacuum dried to obtain 4-(imidazo[4,5-c]-pyridin-1-yl)aniline as a white solid. This product was used in process C without further purification.

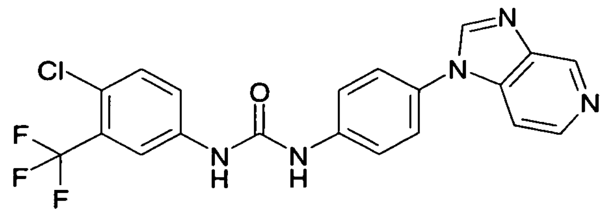
[0144]

Step C

Preparation of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 1)

[0145]

[Formula 20]



[0146]

The 4-(imidazo[4,5-c]pyridin-1-yl)aniline prepared in Step B was dissolved in 10 mL of dichloromethane, and 30 mg (0.137 mmol) of 4-chloro-3-(trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for three hours. The solvent was distilled under reduce pressure, and the obtained crude product was recrystallized from ethyl acetate to obtain 35.0 mg (51%) of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 1) as a colorless crystal.

[0147]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.62-7.76(7H,m), 8.14(1H,d,J=2.0 Hz), 8.43(1H,d,J=5.6 Hz), 8.70(1H,s), 9.09(1H,s), 9.18(1H,s), 9.28(1H,s) ESI (LC-MS positive mode) m/z 431.9 (M+H)

[Example 2]

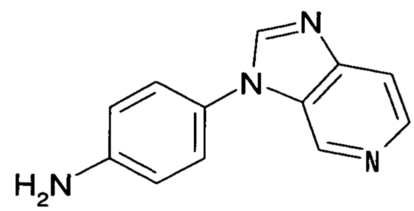
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-c]pyridin-3-ylphenyl)urea (Table 1, Compound No. 2)

Step A

Preparation of 4-(imidazo[4,5-c]pyridin-3-yl)aniline

[0148]

[Formula 21]



[0149]

In 10 mL of methanol, 15.9 mg (0.066 mmol) of 4-nitrophenyl-3H-imidazo[4,5-c]pyridine prepared in Step A of Example 1 was dissolved and the solution was stirred on 5 mg of 10% palladium carbon in a hydrogen atmosphere at room temperature at normal pressures for one hour. After removal of the palladium carbon by filtration, the solvent was distilled under reduced pressure, and the residue was vacuum dried to obtain 4-(imidazo[4,5-c]pyridin-3-yl)-aniline as a white solid. The product was used in Step B without further purification.

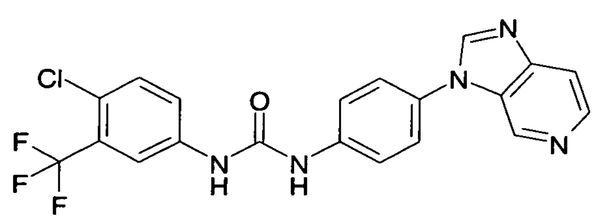
[0150]

Step B

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-imidazo[4,5-c]pyridin-3-ylphenyl)urea (Table 1, Compound No. 2)

[0151]

[Formula 22]



[0152]

The 4-(imidazo[4,5-c]pyridin-3-yl)aniline prepared in

Step A was dissolved in 10 mL of dichloromethane, and 14.2 mg (0.064 mmol) of 4-chloro-3-(trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for three hours. The solvent was distilled under reduced pressure, and the obtained crude product was recrystallized from ethyl acetate to obtain 20.2 g (73%) of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-imidazo[4,5-c]pyridin-3-ylphenyl)urea (Table 1, Compound No. 2) as a colorless crystal.

[0153]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.63-7.80(7H,m), 8.14(1H,d,J=2.0 Hz), 8.43(1H,d,J=5.6 Hz), 8.77(1H,s), 8.98(1H,s), 9.18(1H,s), 9.28(1H,s), 9.29(1H,s)

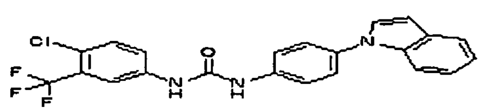
ESI (LC-MS positive mode) m/z 431.9 (M+H)

[Example 3]

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-indol-1-ylphenyl)urea (Table 1, Compound No. 3)

[0154]

[Formula 23]



[0155]

The titled compound can be synthesized from indole, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by using the same techniques as in Example 1.

[0156]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.68(1H,d,J=3.3 Hz), 7.03-7.20(7H,m), 7.50(2H,d,J=8.6 Hz), 7.60-7.70(7H,m), 8.14(1H,d,J=1.0 Hz), 9.06(1H,s), 9.24(1H,s)

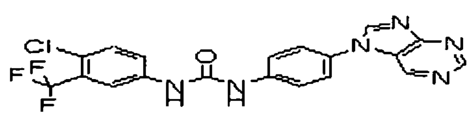
ESI (LC-MS positive mode) m/z 431.9 (M+H)

[Example 4]

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-purin-7-ylphenyl)urea (Table 1, Compound No. 4)

[0157]

[Formula 24]



[0158]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0159]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.62-7.67(3H,m), 7.73(3H,s), 8.12(1H,m), 9.08(2H,d,J=5.3 Hz), 9.21(1H,s), 9.36(1H,s), 9.50 (1H,s)

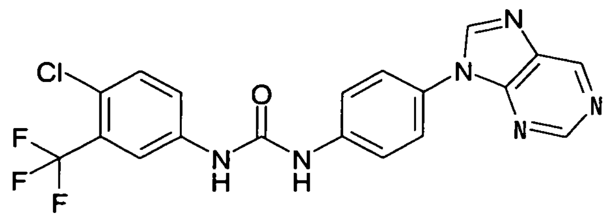
ESI (LC-MS positive mode) m/z 433 (M+H)

[Example 5]

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-purin-9-ylphenyl)urea (Table 1, Compound No. 5)

[0160]

[Formula 25]



[0161]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0162]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.63(2H,m), 7.85(4H,dd,J=23.8, 11.8 Hz), 8.08(1H,d,J=3.7 Hz), 8.39(1H,s), 9.02(1H,s), 9.17(1H,s), 9.28(1H,s), 9.30(1H,s)

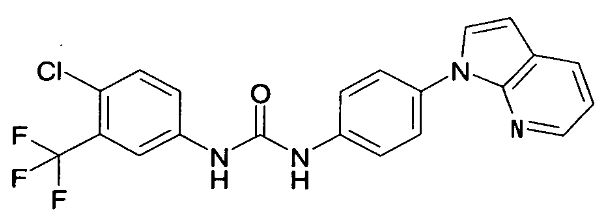
ESI (LC-MS positive mode) m/z 433 (M+H)

[Example 6]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-pyrrolo-[2,3-b]pyridin-1-ylphenyl)urea (Table 1, Compound No.6)

[0163]

[Formula 26]



[0164]

The title compound can be synthesized from pyrrolo[2,3-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same

techniques as in Example 1.

[0165]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.70 (1H,d,J=3.6 Hz), 7.19(1H,dd,J=7.9, 4.8 Hz), 7.58-7.66(4H,m), 7.80(2H,d,J=8.9 Hz), 7.89(1H,d,J=3.7 Hz), 8.04-8.13(2H,m), 8.30(1H,s), 9.02(1H,s), 9.22(1H,s)

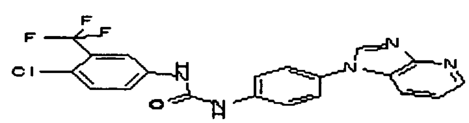
ESI (LC-MS positive mode) m/z 431 (M+H)

[Example 7]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-[4,5-b]pyridin-1-ylphenyl)urea (Table 1, Compound No. 7)

[0166]

[Formula 27]



[0167]

The title compound can be synthesized from imidazo[4,5-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0168]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.39(1H,dd,J=4.6, 7.9 Hz), 7.60-7.70(4H,m), 7.85(2H,d,J=8.9 Hz), 8.13(1H,m), 8.20(1H,m), 8.43(2H,m), 8.85(1H,s), 9.11(1H,s), 9.25(1H,s)

ESI (LC-MS positive mode) m/z 432 (M+H)

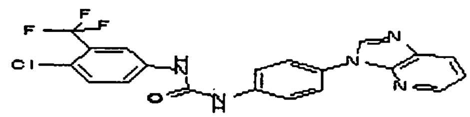
[Example 8]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo-

[4,5-b]pyridin-3-ylphenyl)urea (Table 1, Compound No. 8)

[0169]

[Formula 28]



[0170]

The title compound can be synthesized from imidazo[4,5-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0171]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.37(1H,dd,J=4.9, 8.2 Hz), 7.60-7.75(6H,m), 8.05(1H,dd,J=1.3, 7.9 Hz), 8.14(1H,d,J=2.3 Hz), 8.51(1H,dd,J=1.7, 5.0 Hz), 8.81(1H,s), 9.17(1H,s), 9.28(1H,s)

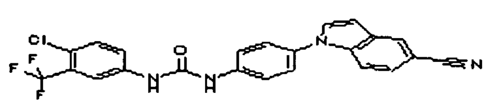
ESI (LC-MS positive mode) m/z 432 (M+H)

[Example 9]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cyanoindol-1-yl)phenyl]urea (Table 1, Compound No. 9)

[0172]

[Formula 29]



[0173]

The title compound can be synthesized from 5-cyanoindole, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same

techniques as in Example 1.

[0174]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.85(1H,d,J=3.3 Hz), 7.50-7.56(3H,m), 7.60-7.72(5H,m), 7.83(1H,d,J=3.3 Hz), 8.13(1H,d,J=2.3 Hz), 8.21(1H,d,J=0.7 Hz), 9.12(1H,s), 9.24(1H,s)

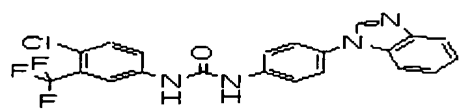
ESI (LC-MS positive mode) m/z 455 (M+H)

Example 10

1-(4-Benzimdazol-1-ylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (Table 1, Compound No. 10)

[0175]

[Formula 30]



[0176]

The title compound can be synthesized from benzimidazole, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 1.

[0177]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.28-7.33(2H,m), 7.55-7.80(8H,m), 8.14(1H,d,J=0.8 Hz), 8.51(1H,s), 9.14(1H,s), 9.28(1H,s)

ESI (LC-MS positive mode) m/z 431 (M+H)

[Example 11]

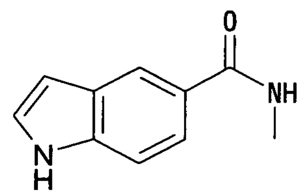
1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indole-5-carboxylic acid methylamide (Table 1, Compound No. 11)

Step A

Preparation of 1H-indole-5-carboxylic acid methylamide

[0178]

[Formula 31]



[0179]

In 5 mL of N,N-dimethylformamide, 500 mg (3.1 mmol) of 1H-indole-5-carboxylic acid, 750 mg (9.3 mmol) of 40% methylamine, 477 mg (3.1 mmol) of benzotriazole-1-ol hydrate and 713 mg (3.8 mmol) of (3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride were dissolved and the solution was stirred at room temperature for three hours, and then the solvent was distilled under reduced pressure. The obtained residue was dissolved in ethyl acetate and washed with a saturated sodium hydrogencarbonate solution (50 mL, twice) and a saturated saline (50 mL) in the order named. The organic layer was dried and then concentrated to obtain 397 mg (73%) of a crude product of 1H-indole-5-carboxylic acid methylamide. The product was used in the next reaction without further purification.

[0180]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.01(3H,d,J=4.9 Hz), 6.20(1H,br.s), 6.59(1H,br.s), 7.20-7.22(2H,m), 7.37(1H,d,J=8.6 Hz), 7.60(1H,d,J=8.6 Hz), 8.07(1H,s), 8.64(1H,br.s),

ESI (LC-MS positive mode) m/z 175 (M+H)

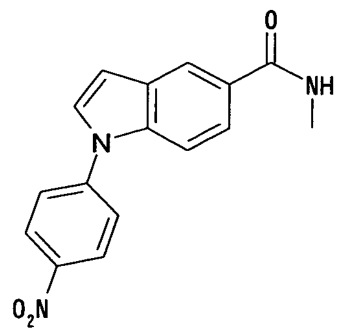
[0181]

Step B

Preparation of 1-(4-nitrophenyl)-1H-insole-5-carboxylic acid methylamide

[0182]

[Formula 32]



[0183]

The title compound can be synthesized from 1H-indole-5-carboxylic acid methylamide and 4-fluoronitro-benzene in the same manner as in Step A of Example 1.

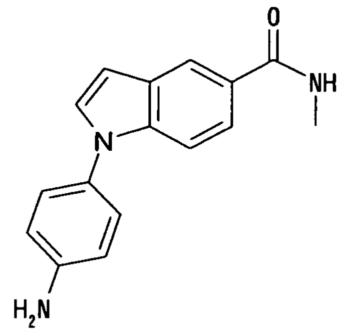
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.84(3H,d,J=4.8 Hz), 6.93(1H,d,J=3.3 Hz), 7.80(2H,s), 7.90-8.00(3H,m), 8.24(1H,s), 8.42-8.50(3H,m)

Step C

Preparation of 1-(4-aminophenyl)-1H-indole-5-carboxylic acid methylamide

[0184]

[Formula 33]



[0185]

The title compound can be synthesized from 1-(4-nitrophenyl)-1H-indole-5-carboxylic acid methylamide in the same manner as in Step B of Example 1.

^{1}H-NMR (270 MHz, CD_3OD) δ (ppm): 2.95(3H,d,J=4.8 Hz), 6.78(1H,d,J=3.3 Hz), 6.86(2H,d,J=9.6 Hz), 7.21(2H,d,J=9.6 Hz), 7.38-7.41(2H,m), 7.62(1H,dd,J=1.6, 8.5 Hz), 8.13(1H,d,J=1.3 Hz), 8.34(1H,br.s),

ESI (LC-MS positive mode) m/z 266 (M+H)

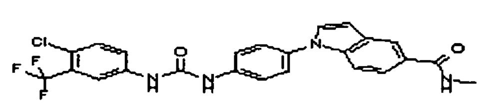
[0186]

Step D

Preparation of 1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-indole-5-carboxylic acid methylamide (Table 1, Compound No. 11)

[0187]

[Formula 34]



[0188]

The title compound can be synthesized from 1-(4-aminophenyl)-1H-indole-5-carboxylic acid methylamide and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same

manner as in Step C in Example 1.

[0189]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.81(3H,d,J=4.3 Hz), 6.79 (1H,d,J=3.3 Hz), 7.50-7.55(3H,m), 7.63-7.75(6H,m), 8.14(1H,d,J=2.0 Hz), 8.20(1H,d,J=0.7 Hz), 8.38(1H,q,J=4.3 Hz), 9.09(1H,s), 9.24(1H,s)

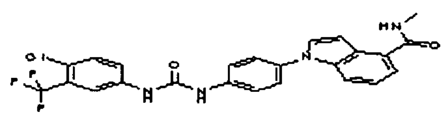
ESI (LC-MS positive mode) m/z 487 (M+H)

[Example 12]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indole-4-carboxylic acid methylamide (Table 1, Compound No. 12)

[0190]

[Formula 35]



[0191]

The title compound can be synthesized from 1H-indole-4-carboxylic acid, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0192]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.84(3H,d,J=4.3 Hz), 7.09 (1H,d,J=3.3 Hz), 7.23(1H,dd,J=8.3, 7.6 Hz), 7.47-7.53(3H,m), 7.60-7.75(6H,m), 8.14(1H,d,J=2.0 Hz), 8.29(1H,t,J=4.3 Hz), 9.08(1H,s), 9.24(1H,s)

ESI (LC-MS positive mode) m/z 487.2 (M+H)

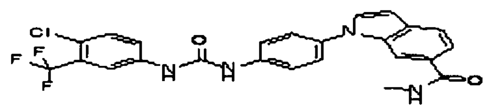
[Example 13]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-

phenyl}-1H-indole-6-carboxylic acid methylamide (Table 1, Compound No. 13)

[0193]

[Formula 36]



[0194]

The title compound can be synthesized from 1H-indole-6-carboxylic acid, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0195]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.88(3H,d,J=4.3 Hz), 6.73(1H,d,J=3.0 Hz), 7.55(2H,d,J=8.9 Hz), 7.60-7.76(7H,m), 8.00(1H,s), 8.14(1H,d,J=2.3 Hz), 8.40(1H,t,J=4.3 Hz), 9.10(1H,s), 9.26(1H,s)

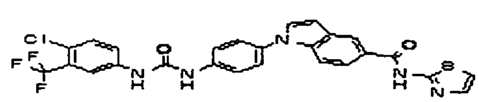
ESI (LC-MS positive mode) m/z 487.0 (M+H)

[Example 14]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-indole-5-carboxylic acid thiazol-2-ylamide (Table 1, Compound No. 14)

[0196]

[Formula 37]



[0197]

The title compound can be synthesized from 1H-indole-4-carboxylic acid, 4-fluoronitrobenzene, 2-aminothiazole

and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0198]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.52(1H,s), 7.12(1H,d,J=4.3 Hz), 7.39-7.40(2H,m), 7.60-7.75(7H,m), 7.85(1H,d,J=8.6 Hz), 8.16(1H,s), 8.31(1H,s), 9.23(1H,s), 9.39(1H,s), 11.30(1H,s)

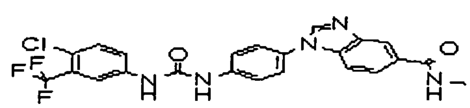
ESI (LC-MS positive mode) m/z 556 (M+H)

[Example 15]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-benzimidazole-5-carboxylic acid methylamide (Table 1, Compound No. 15)

[0199]

[Formula 38]



[0200]

The title compound can be synthesized from 1H-benzimdazole-5-carboxylic acid, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 11.

[0201]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.82(3H,d,J=2.7 Hz), 7.76-7.90(8H,m), 8.17(1H,br.d, J=1.0 Hz), 8.30(1H,s), 8.50(1H,br.s), 8.61(1H,s), 9.45(1H,br.s), 9.60(1H,br.s)

ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 16]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-2-

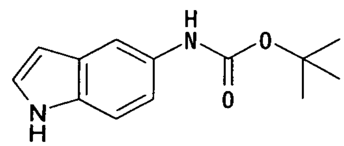
fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 16)

Step A

Preparation of (1H-indole-5-yl)carbamic acid tert-Butyl ester

[0202]

[Formula 39]



[0203]

In 100 mL of methanol, 2.64 g (20 mmol) of 5-aminoindole was dissolved, and 4.15 mL (30 mmol) of triethylamine and 5.23 g (24 mmol) of Boc_2O were added thereto and the mixture solution was stirred at room temperature for six hours. The reaction solution was concentrated under reduced pressure, and the residue was distributed with ethyl acetate (200 mL) and water (100 mL), and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the residue was distributed between ethyl acetate (200 mL) and water (100 mL) and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the residue was purified by a silica gel column (Wako Gel C200: 300 g, n-hexane:ethyl acetate=4:1) to obtain 4.38 g (94%) of (1H-

indol-5-yl)carbamic acid tert-butyl ester as a white solid.

[0204]

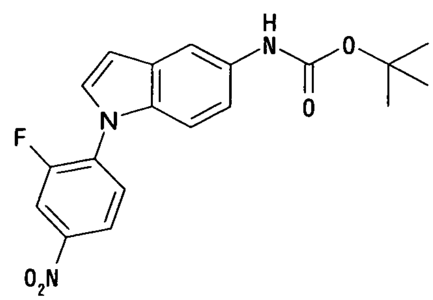
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.43(9H,s), 6.38(1H,br.s), 6.29-6.33(1H,m), 7.04(1H,dd,J=2.3, 8.9 Hz), 7.19(1H,s), 7.23(1H,d,J=8.9 Hz), 7.61(1H,br.s)

Step B

Preparation of [1-(2-fluoro-4-nitrophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester

[0205]

[Formula 40]



[0206]

The title compound can be synthesized from (1H-indol-5-yl)carbamic acid tert-butyl ester and 3,4-difluoro-nitroenzene in the same manner as in Step A of Example 1.

[0207]

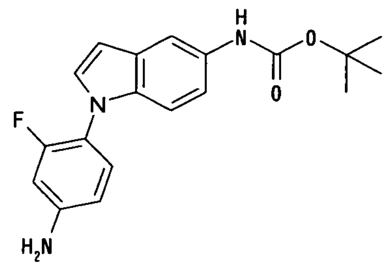
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.49(9H,s), 6.74(1H,d,J=3.3 Hz), 7.29 (2H,s), 7.62(1H,t,J=3.3 Hz), 7.82(1H,br.s), 7.96(1H,dd,J=8.6, 8.7 Hz), 8.23-8.29(1H,m), 9.23 (1H,s), 9.26(1H,br.s)

Step C

Preparation of [1-(4-amino-2-fluorophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester

[0208]

[Formula 41]



[0209]

The title compound can be synthesized from [1-(2-fluoro-4-nitrophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester in the same manner as in step B of Example 1.

[0210]

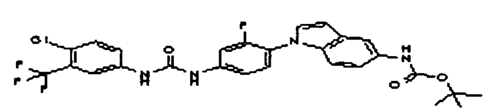
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.49(9H,s), 6.40-6.58(4H,m), 7.04-7.20(4H,m), 7.69(1H,br.s)

<u>Step D</u>

Preparation of 1-{4-[3-(4-Chloro-3-(trifluoromethyl-phenyl)ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 16)

[0211]

[Formula 42]



[0212]

The title compound can be synthesized from [1-(4-amino—2-fluorophenyl)-1H-indol-5-yl)carbamic acid tert-butyl ester and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Step C of Example 1.

[0213]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.58(9H,s),

6.60(1H,d,J=3.3 Hz), 7.60(1H, d, J=8.9 Hz),
7.21(1H,d,J=0.8 Hz), 7.34(1H,dd,J=0.8, 9.2 Hz),
7.42-7.54(2H,m), 7.62-7.78(4H,m), 8.12(1H,d,J=1.3 Hz),
9.18(1H,s), 9.28(1H,s), 9.33(1H,s)

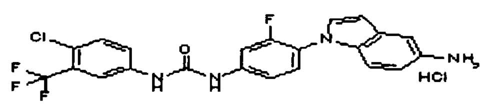
ESI (LC-MS positive mode) m/z 563.0 (M+H)

[Example 17]

1-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 17)

[0214]

[Formula 43]



[0215]

In 2 mL of ethyl acetate, 104 mg (0.18 mmol) of (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester was dissolved, and 2 mL of a 4N hydrogen chloride ethyl acetate solution was added thereto and the mixture solution was stirred at room temperature for one hour. The reaction solution was concentrated and the obtained product was triturated with ethyl acetate to obtain 80 mg (86%) of 1-[4-(5-aminoindol-1-yl)-3-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 17).

[0216]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.80(1H,d,J=2.6 Hz),
7.17(1H, d, J=8.9 Hz), 7.29(1H,d,J=8.9 Hz),

7.34(1H,d,J=9.2 Hz), 7.55(1H,t,J=8.9 Hz), 7.67(4H,m), 7.78(1H,d,J=13.2 Hz), 8.14(1H,s), 9.74(1H,br.s), 9.78(1H, br.s), 10.00(2H,br.s)

ESI (LC-MS positive mode) m/z 463.2 (M+H)

[Example 18]

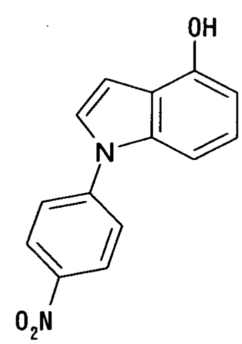
Acetic acid 1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-indol-4-yl ester (Table 1, Compound No. 18)

Step A

Preparation of 1-(4-nitrophenyl)-1H-indole-4-ol

[0217]

[Formula 44]



[0218]

The title compound can be synthesized from 1H-indole-4-ol and 4-fluoronitrobenze in the same manner as in Step A of Example 1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.11-6.14(1H,m), 6.82(1H,dd,J=0.7, 7.6 Hz), 6.59(1H,br.s), 7.06-7.10(2H,m), 7.16(1H,t,J=7.9 Hz), 7.34-7.38(2H,m), 8.20-8.28(2H,m), 11.45(1H,br.s)

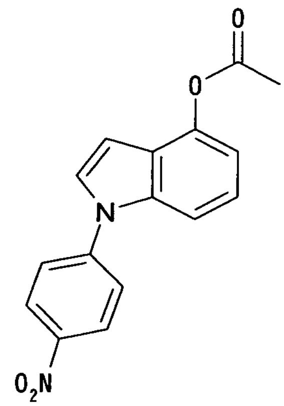
Step B

Preparation of Acetic acid 1-(4-nitrophenyl)-1H-

indol-4-yl ester

[0219]

[Formula 45]



[0220]

In 8 mL of methylene chloride, 387 mg (1.52 mmol) of 1-(4-nitrophenyl)-1H-indole-4-ol was dissolved, and 0.186 mL (2.00 mmol) of acetic anhydride and 0.318 mL (2.28 mmol) of triethylamine were added thereto and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was distributed between methylene chloride (50 mL) and a saturated ammonium chloride aqueous solution (20 mL) and washed with a saturated sodium chloride solution, and the organic layer was dried and then concentrated under reduced pressure to obtain acetic acid 1-(4- nitrophenyl)-1H-indol-4-yl ester. The product was used in the next reaction without further purification.

[0221]

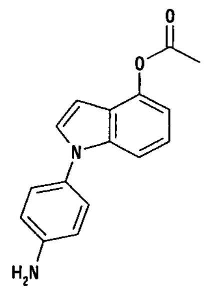
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 2.66(3H,s), 6.47-6.49(1H,m), 6.97-7.07(3H,m), 7.16-7.41(3H,m), 8.12-8.22(2H,m), 8.37(1H,d,J=8.6 Hz)

<u>Step C</u>

Preparation of acetic acid 1-(4-aminophenyl)-1H-indol-4-yl ester

[0222]

[Formula 46]



[0223]

The title compound can be synthesized from acetic acid 1-(4-nitrophenyl)-1H-indol-4-yl ester in the same manner as in Step B of Example 1.

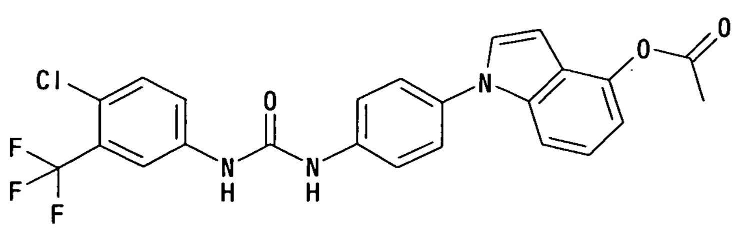
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 2.65(3H,s), 3.59(2H,s), 6.65-6.71(5H,m), 7.05-7.16(1H,m), 7.20(1H,d,J=3.2 Hz), 7.35(1H,d,J=2.7 Hz), 8.12(1H,d,J=5.5 Hz)

<u>Step D</u>

Preparation of acetic acid 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indol-4-yl ester

[0224]

[Formula 47]



[0225]

The title compound can be synthesized from acetic

acid 1-(4-aminophenyl)-1H-indol-4-yl ester and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Step C of Example 1.

[0226]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.66(3H,s), 6.60(1H,d,J=3.5 Hz), 6.75(1H, d, J=8.1 Hz), 6.99(2H,d,J=8.9 Hz), 7.28(1H,t,J=8.3 Hz), 7.45(2H,d,J=8.9 Hz), 7.60(2H,m), 7.82(1H,d,J=4.1 Hz), 8.11(2H,m), 8.82(1H,s), 9.12(1H,s)

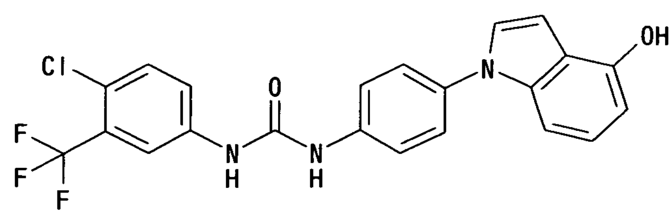
ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 19]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-hydroxyindol-1-yl)phenyl]urea (Table 1, Compound No. 19)

[0227]

[Formula 48]



[0228]

In 3 mL of tetrahydrofuran, 60 mg (0.12 mmol) of acetic acid 1-{4-[3-(4-chloro-3-(trifluoromthyl)phenyl)-ureido]phenyl}-1H-indol-4-yl ester was dissolved, and 1 mL of a 1N sodium hydroxide aqueous solution was added thereto and the mixture solution was stirred at room temperature for two hours. The reaction solution was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The

organic layer was washed with a saturated sodium chloride solution, dried and then concentrated under reduced pressure, and the obtained residue was recrystallized from ethyl acetate to obtain 17 mg (31%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-hydroxyindol-1-yl)phenyl]urea (Table 1, Compound No. 19) as a white solid.

[0229]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.21(1H,br), 6.48(1H,d,J=8.1 Hz), 6.63(1H,s), 6.89(4H,s), 6.95-7.02(2H,m), 7.05(1H,d,J=8.0 Hz), 7.19 (1H,d,J=8.9 Hz), 7.25(1H,t,J=3.0 Hz), 7.43(2H,d,J=8.6 Hz), 8.11(1H,s), 9.12(1H,s), 11.24(1H,s)

ESI (LC-MS positive mode) m/z 446 (M+H)

[Example 20]

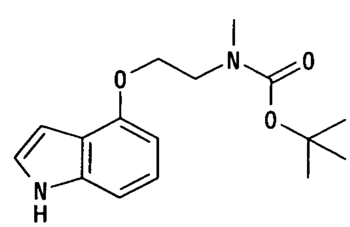
[2-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester (Table 1, Compound No. 20)

Step A

Preparation of [2-(1H-indol-4-yloxy)ethyl]-methyl-carbamic acid tert-butyl ester

[0230]

[Formula 49]



[0231]

In 50 mL of tetrahydrofuran, 200 mg (1.51 mmol) of

1H-indole-4-ol and 527 mg (3.00 mmol) of 2-hydroxyethyl-methylcarbamic acid tert-butyl ester were dissolved, and 1.51 mL (3.00 mmol) of a diethyl azodicarboxylate 40% toluene solution and 788 mg (3.00 mmol) of triphenyl-phosphine were added thereto and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was concentrated, and then distributed between ethyl acetate and a saturated ammonium chloride aqueous solution. The organic layer was washed with a saturated sodium chloride solution, dried and concentrated, and the obtained residue was purified by a silica gel column (50g, n-hexane:ethyl acetate=2:1) to obtain 433 mg (99%) of [2-(1H-indol-4-yloxy)ethyl]-methyl-carbamic acid tert-butyl ester as a viscous oily substance.

[0232]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.48(9H,s), 3.06(3H,s), 3.70(2H,br.s), 4.52(2H,br.s), 6.50(1H,d,J=7.3 Hz), 6.63(1H,t,J=2.1 Hz), 7.02-7.15(3H,m), 8.19(1H,br.s)

ESI (LC-MS positive mode) m/z 291 (M+H)

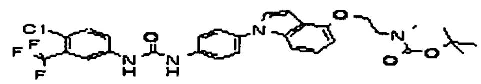
[0233]

Step B

[2-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester (Table 1, Compound No. 20)

[0234]

[Formula 50]



[0235]

The title compound can be synthesized from [2-(1H-indol-4-yloxy)ethyl]-methylcarbamic acid tert-butyl ester, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by using the same techniques as in Example 1.

[0236]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.38(9H,d,J=11.3 Hz), 2.94(2H,d,J=6.8 Hz), 3.63(2H,t,J=5.4 Hz), 4.22(2H,br), 6.63(1H,d,J=3.0 Hz), 6.65(1H,br), 7.10 (2H,d,J=4.5 Hz), 7.48(3H,m), 7.63-7.70(4H,m), 8.13(1H,d,J=2.7 Hz), 9.12(1H,br), 9.30(1H,br)

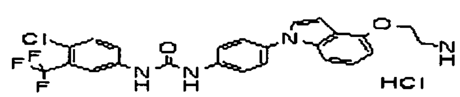
ESI (LC-MS positive mode) m/z 603 (M+H)

[Example 21]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-methylamino-ethoxy)-indol-1-yl]phenyl}urea hydrochloride (Table 1, Compound No. 21)

[0237]

[Formula 51]



[0238]

In 5 ml of a 4N hydrogen chloride ethyl acetate solution, 200 mg (0.33 mmol) of [2-(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-indol-4-yloxy)-ethyl]-methylcarbamic acid tert-butyl ester was dissolved

and the solution was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and then the obtained residue was triturated with ethyl acetate to obtain 110 mg (66%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-methyl-amino-ethoxy)-indol-1-yl]phenyl}urea hydrochloride.

[0239]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 2.71(3H,t,J=5.4 Hz), 3.42(2H,br.s), 4.39(2H,t,J=4.8 Hz), 6.68(1H,dd,J=6.8, 1.6 Hz), 6.85(1H,d,J=3.5 Hz), 7.08-7.17(2H,m), 7.48(2H,d,J=8.7 Hz), 7.53(1H,d,J=2.9 Hz), 7.65-7.70(4H,m), 8.14(1H,d,J=2.1 Hz), 9.48(1H,s), 9.74(1H,s)

ESI (LC-MS positive mode) m/z 503 (M+H)

[Example 22]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-morpholin-4-yl-ethoxy]indol-1-yl]phenyl}urea (Table 1, Compound No. 22)

[0240]

[Formula 52]

[0241]

The title compound can be synthesized from 1H-indole-4-ol, 2-morpholin-4-ylethanol, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Example 20.

[0242]

^{1}H-NMR (270 MHz, $CDCl_3$) δ(ppm): 2.68(4H,t,J=4.6 Hz),

2.94(2H,t,J=5.4 Hz), 3.76(4H,t,J=4.6 Hz), 4.32(2H,t,J=5.4 Hz), 6.58(1H,t,J=4.1 Hz), 6.70(1H,s), 6.77(1H,d,J=3.2 Hz), 6.81(1H,s), 7.12(2H,d,J=4.9 Hz), 7.19(1H,d,J=3.2 Hz), 7.43-7.51(5H,m), 7.63(1H,d,J=7.3 Hz), 7.73 (1H,d,J=2.4 Hz)

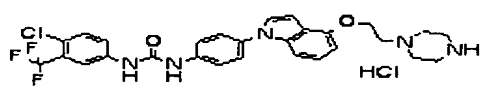
ESI (LC-MS positive mode)m/z 559(M+H)

[Example 23]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[4-(2-piperazin-1-yl-ethoxy]-indol-1-yl]phenyl}urea (Table 1, Compound No. 23)

[0243]

[Formula 53]



[0244]

The title compound can be synthesized from 1H-indole-4-ol, 4-(2-hydroxyethyl)piperazine-1-carboxylic acid tert-butyl ester, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Example 20 and Example 21.

[0245]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.10-3.80(10H,br.s), 4.53(2H,br.s), 6.68(1H,dd,J=6.8, 1.6 Hz), 6.80(1H,d,J=3.5 Hz), 7.08-7.18(2H,m), 7.48(2H,d,J=8.7 Hz), 7.53(1H,d,J=2.9 Hz), 7.65-7.70(4H,m), 8.14(1H,d,J=2.1 Hz), 9.42(1H,s), 9.66(1H,s)

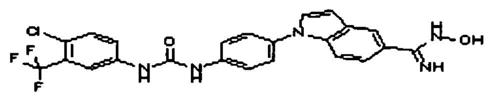
ESI (LC-MS positive mode) m/z 558 (M+H)

[Example 24]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-N-hydroxy-1H-indole-5-carboxamidine (Table 1, Compound No. 24)

[0246]

[Formula 54]



[0247]

In 10 mL of ethanol, 91 mg (0.20 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cycanoindol-1-yl)phenyl]urea was dissolved, and 109 μL (o.79 mmol) of triethylamine and 55 mg (0.79 mmol) of hydroxylamine hydrochloride were added thereto, and the mixture solution was heated and refluxed for 5 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the obtained residue was recrystallized from methanol to obtain 51.6 mg (53%) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine (Table 1, Compound No. 24).

[0248]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 5.78(2H,br.s), 6.72(1H,d,J=3.3 Hz), 7.45-7.68(10H,m), 7.96(1H,s), 8.14(1H,d,J=2.0 Hz), 9.08(1H,s), 9.23(1H,s), 9.47(1H,s)

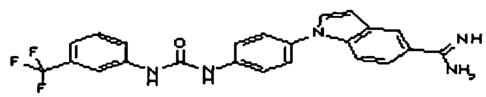
ESI (LC-MS positive mode) m/z 488.5 (M+H)

[Example 25]

1-{4-[3-(3-(Trifluoromethyl)phenyl)ureido]phenyl}-1H-indole-5-carboxamidine (Table 1, Compound No. 25)

[0249]

[Formula 55]



[0250]

In 10 mL of methanol, 12 mg (0.025 mmol) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine was dissolved and the solution was subjected to hydrogenation catalytic reduction on 10 % palladium carbon in a hydrogen atmosphere at room temperature for 14 hours. After removal of the palladium carbon by a membrane filter, the filtrate was concentrated under reduced pressure, and the obtained product was triturated from diethyl ether to obtain 3 mg (25%) of 1-{4-[3-(3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-indole-5-carboxamidine (Table 1, Compound No. 25).

[0251]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.90-6.98(1H,m), 7.25-7.35(2H,m), 7.45-7.85(8H,m), 8.03(1H,d,J=4.9 Hz), 8.24(1H,s), 8.49(1H,s), 8.62(0.5H,s), 8.79(0.5H,s), 8.93(0.5H,s), 9.09(0.5H,s), 9.24(0.5H,s), 9.34(0.5H,s), 9.38(0.5H), 9.47(0.5H,s)

ESI (LC-MS positive mode) m/z 438 (M+H)

[Example 26]

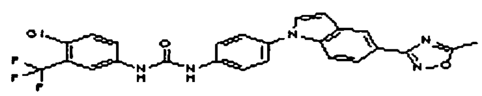
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[5-(5-

methyl-[1,2,4]oxadiazol-3-yl)indol-1-yl]phenyl}urea

(Table 1, Compound No. 26)

[0252]

[Formula 56]



[0253]

In 0.2 mL of pyridine, 10.5 mg (0.022 mmol) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine was dissolved, and 10 mg (0.098 mmol) of acetic anhydride was added thereto, and the mixture solution was stirred at 80°C for 14 hours. The reaction solution was concentrated under reduced pressure, and then the obtained residue was purified by Megabond Elute Silica Gel (a product of Varian, 1g, methylene chloride:methanol=20:1) to obtain 4.1 mg (37%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-{4-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)indol-1-yl]phenyl}urea (Table 1, Compound No. 26).

[0254]

^{1}H-NMR (270 MHz, CD_3ODO) δ (ppm): 2.68(3H,s), 6.78(1H,d,J=3.3 Hz), 7.45-7.53(3H,m), 7.55-7.68(5H,m), 7.87(1H,dd,J=1.7, 8.6 Hz), 7.96(1H,d,J=2.3 Hz), 8.37(1H,d,J=1.3 Hz),

ESI (LC-MS positive mode) m/z 512.0 (M+H)

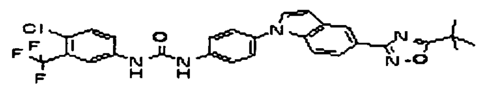
[Example 27]

1-{4-[5-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)indol-1-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)urea

(Table 1, Compound No. 27)

[0255]

[Formula 57]



[0256]

The title compound can be synthesized from 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-hydroxy-1H-indole-5-carboxamidine and pivalic anhydride by using the same techniques as in Example 26.

[0257]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.44(9H,s), 6.63(1H,d,J=3.3 Hz), 7.13(1H,d,J=3.0 Hz), 7.20-7.40(7H,m), 7.50(1H,dd,J=2.3, 8.5 Hz), 7.58(1H,d,J=2.3 Hz), 7.62(1H,br.s), 7.78(1H,dd,J=1.7, 8.6 hz), 8.36(1H,d,J=1.3 Hz)

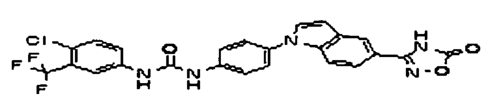
ESI (LC-MS positive mode) m/z 554 (M+H)

[Example 28]

1-(4-Chloro-3-fluoromethyl)phenyl)-3-{4-[5-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)indol-1-yl]-phenyl}urea (Table 1, Compound No. 28)

[0258]

[Formula 58]



[0259]

The title compound can be synthesized from 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-

hydroxy-1H-indole-5-carboxamidine and ethyl chloroformate by using the same techniques as in Example 26.

[0260]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.84(1H,d,J=3.2 Hz), 7.55(1H,d,J=8.4 Hz), 7.65-7.71(6H,m), 7.77(1H,d,J=3.2 Hz), 8.14-8.16 (2H,m), 9.13(1H,s), 9.26(1H,s)

ESI (LC-MS positive mode) m/z 514.0 (M+H)

[Example 29]

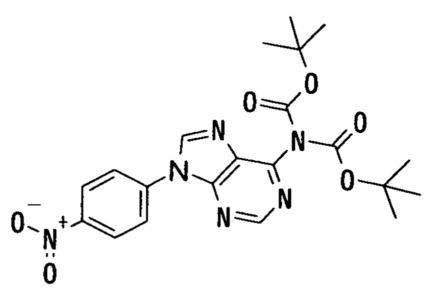
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}urea (Table 1, Compound No. 29)

Step A

Preparation of 6-di-tert-butoxycarbonylamino-9-(4-nitrophenyl)-9H-purine

[0261]

[Formula 59]



[0262]

In 100 mL of dimethyl sulfoxide, 4.05 g (30.0 mmol) of adenine was dissolved, and 3.5 g (31.0 mmol) of potassium tert-butoxide and 5.0 g (35.0 mmol) of 4-fluoronitrobenzene were added thereto and the mixture solution was stirred at 80°C for three hours. The solution was diluted with 200 mL of water, and the formed

precipitate was collected by filtration, washed with water, and vacuum dried. The obtained product (6.66 g) dissolved in 20 mL of dimethyl sulfoxide, and 17.1 g (78.0 mmol) and 0.35 g (2.86 mmol) of 4-dimethylaminopyridine were added thereto, and the mixture solution was stirred at room temperature for six hours. The reaction solution was distributed between ethyl acetate and a saturated sodium chloride solution, and the organic layer was further washed with a saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue was separated by a silica gel column (Wako Gel C-200: 300 g, n-hexane:ethyl acetate=2:1) to obtain 7.86 g (57%) of 6-di-tert-butoxycarbonylamino-9-(4-nitrophenyl)-9H-purine as a white solid.

[0263]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50(9H,s), 1.56(9H,s), 8.09(2H,d,J=8.4 Hz), 8.45-8.52(3H,m), 8.98(1H,s)

ESI (LC-MS positive mode) m/z 457 (M+H)

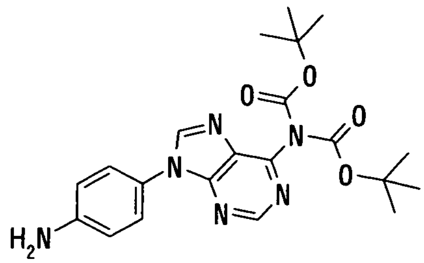
[0264]

Step B

Preparation of 9-(4-aminophenyl)6-di-tert-butoxy-carbonylamino–9H-purine

[0265]

[Formula 60]



[0266]

The title compound can be synthesized from 6-di-tert-butoxycarbonylamino-9-(4-nitrophenyl)-9H-prine by using the same techniques as in Step B of Example 1.

ESI (LC-MS positive mode)m/z 427(M+H)

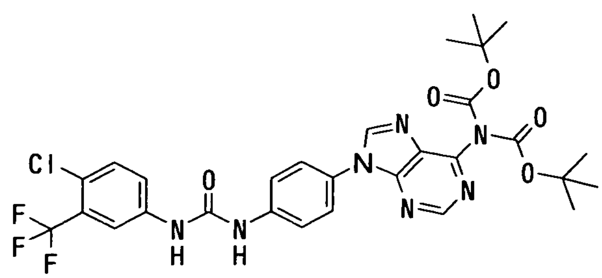
[0267]

Step C

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}urea (Table 1, Compound No. 29)

[0268]

[Formula 61]



[0269]

The title compound can be synthesized from 9-(4-aminophenyl)-6-di-tert-butoxycarbonylamino-9H-purine and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Step C of Example 1.

[0270]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.41(18H,s), 7.65-7.86(6H,m), 8.14(1H,d,J=2.0 Hz), 8.91(1H,s), 9.02(1H,s), 9.18(1H,s), 9.28(1H,s)

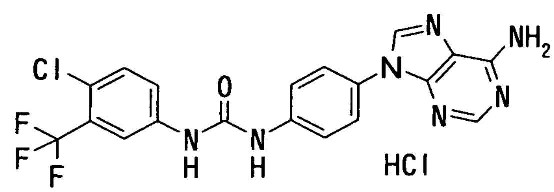
ESI (LC-MS positive mode) m/z 648 (M+H)

[Example 30]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 30)

[0271]

[Formula 62]



[0272]

In a 3 mL of a 4N hydrogen chloride ethyl acetate solution, 32 mg (0.049 mmol) of 1-(4-chloro-3-(trifluoromethyl)-3-{4-[6-(di-tert-butoxycarbonyl amino)purin-9-yl]phenyl}urea was dissolved, and the solution was stirred at room temperature for three hours. After concentrating the reaction solution, the residue was tritulated with diethyl ether to obtain 22 mg (quantitative) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethylphenyl)urea hydrochloride (Table 1, Compound No. 30) as a white solid.

[0273]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(2H,s), 7.71(4H,s), 8.14(1H,s), 8.51(1H,s), 8.82(1H,s),

9.57(1H,s), 9.76(1H,s)

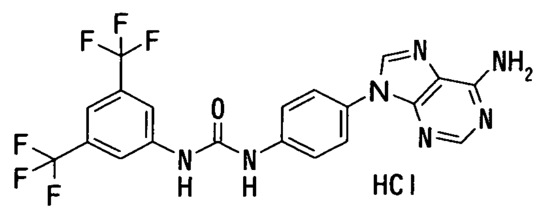
ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 31]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(3,5-bis-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 31)

[0274]

[Formula 63]



[0275]

The title compound can be synthesized from 3,5-bis-(trifluoromethyl)phenyl isocyanate by the same methods as in Examples 29 and 30.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(2H,s), 7.70-7.77(3H,m), 8.14(2H,s), 8.54(1H,s), 8.88(1H,s), 9.57(1H,s), 9.88(1H,s)

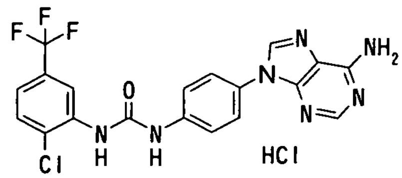
ESI (LC-MS positive mode) m/z 482 (M+H)

[Example 32]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(2-chloro-5-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 32

[0276]

[Formula 64]



[0277]

The title compound can be synthesized from 2-chloro-5-(trifluoromethyl)phenyl isocyanate by the same methods as in Examples 29 and 30.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.29(1H,dd,J=2.0, 8.3 Hz), 7.70-7.77(5H,m), 8.48(1H,s), 8.64(1H,d,J=2.0 Hz), 8.80(1H,s), 8.86(1H,s), 10.19(1H,s)

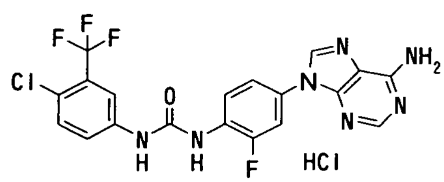
ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 33]

1-[4-(6-Aminopurin-9-yl)-2-fluorophenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 33)

[0278]

[Formula 65]



[0279]

The title compound can be synthesized from adenine, 2,4-difluoronitrobenzene and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by the same method as in Examples 29 and 30.

[0280]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.43-7.60(4H,m),

7.96(1H,d,J=2.0 Hz), 8.14(1H,d,J=5.6, 8.0 Hz),

8.43(2H,s), 8.62(1H,s), 9.95(1H,s)

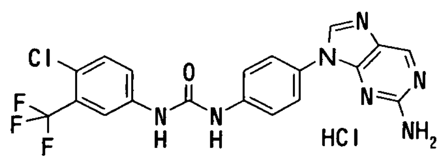
ESI (LC-MS positive mode) m/z 466 (M+H)

[Example 34]

1-[4-(2-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 34)

[0281]

[Formula 66]



[0282]

The title compound can be synthesized from 2-aminopurine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same methods as in Examples 29 and 30.

[0283]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65-7.73(6H,m), 8.12(1H,d,J=2.0 Hz), 8.73(1H,s), 8.96(1H,s), 9.46(1H,s), 9.65(1H,s)

ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 35]

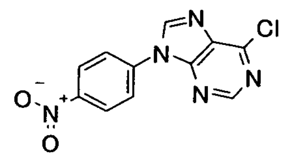
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-methoxy-ethylamino)purin-9-yl]phenyl}urea hydrochloride (Table 1, Compound No. 35)

Step A

Preparation of 6-chloro-9-(4-nitrophenyl)-9H-purine

[0284]

[Formula 67]



[0285]

The title compound can be synthesized from 2-chloropurine and 4-fluoronitrobenzene by the same method as in Step A of Example 1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 8.27-8.33(2H,m), 8.51-8.56(2H,m), 8.95(1H,s), 9.32(1H,s)

ESI (LC-MS positive mode) m/z 276 (M+H)

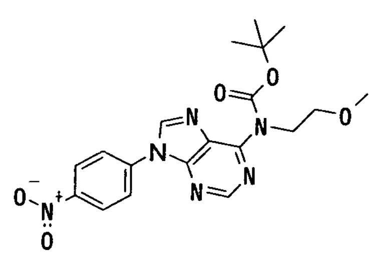
[0286]

Step B

Preparation of (2-methoxyethyl)-[9-(4-nitrophenyl)-9H-purin-6-yl]carbamic acid tert-butyl ester

[0287]

[Formula 68]



[0288]

In 1 mL of isopropanol, 100 mg (0.36 mmol) of 6-chloro-9-(4-nitrophenyl)-9H-purine was dissolved, and 400 mg (5.3 mmol) of 2-methoxyethylamine was added thereto, and the mixtue solution was stirred at 80°C for four hours.

The reaction solution was concentrated under reduced pressure and then distributed between ethyl acetate and a saturated sodium chloride solution. The organic layer was further washed with a saturated sodium chloride solution, dried and then concentrated under reduced pressure. The obtained residue was dissolved in 1 mL of dimethylformamide, and 4 mg (0.525 mmol) of dibutyl dicarbonate and the 114 mg (0.035 mmol) of 4-dimethyl-aminopyridine were added thereto, and the mixture solution was stirred at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by Megabond Elute Silica Gel (5 g, n-hexane:ethyl acetate=1:1) to obtain 118 mg (72%) of (2-methoxyethyl)-[9-(4-nitrophenyl)-9H-purin-6-yl]-carbamic acid tert-butyl ester.

[0289]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.50(9H,s), 3.25(3H,s), 3.65(2H,t,J=5.7 Hz), 3.70(2H,br.s), 7.96(1H,s), 8.27-8.33(2H,m), 8.49-8.52(2H,m), 8.85(1H,s)

ESI (LC-MS positive mode) m/z 315 (M+H)

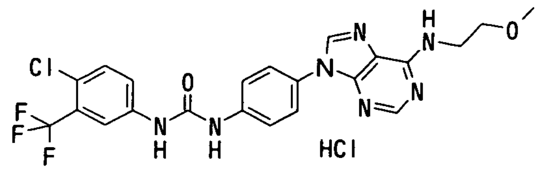
[0290]

Step C

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(2-methoxy-ethylamino)purin-9-yl]-phenyl}urea hydrochloride (Table 1, Compound No. 35)

[0291]

[Formula 69]



[0292]

The title compound can be synthesized from (2-methoxyethyl)-[9-(4-nitrophenyl)-9H-purin-6-yl]carbamic acid tert-butyl ester and 4-chloro-3-(trifluoromethyl)-phenyl isocyanate by the methods of Steps B and C of Example 1 and Example 30.

[0293]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.29(3H,s), 3.59(2H,br.s), 3.73(2H,br.s), 7.60-7.80(7H,m), 8.13(1H,s), 8.40(1H,br.s), 8.72(1H,br.s), 9.50(1H,br.s), 9.70(1H,br.s)

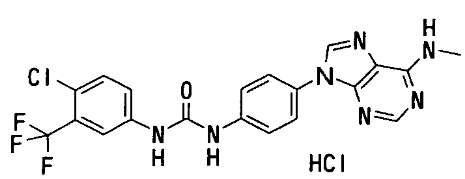
ESI (LC-MS positive mode) m/z 506 (M+H)

[Example 36]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(6-(methylamino)purin-9-yl)phenyl]urea hydrochloride (Table 1, Compound No. 36)

[0294]

[Formula 70]



[0295]

The title compound can be synthesized from 6-chloropurine, methylamine, 4-fluoronitrobenzene and

4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same method as in Example 35.

[0296]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.54(3H,s), 7.60-7.80(7H,m), 8.13(1H,s), 8.46(1H,s), 8.73(1H,s), 9.52(1H,s), 9.72(1H,s)

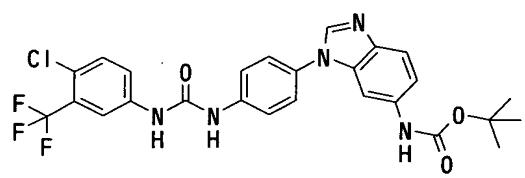
ESI (LC-MS positive mode) m/z 462 (M+H)

[Example 37]

3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-3H-benzimidazol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 37)

[0297]

[Formula 71]



[0298]

The title compound can be synthesized from 6-amino-1H-benzimidazole, di-tert-butyl dicarbonate, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same method as in Example 16.

[0299]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50 (9H,s), 6.87(1H,s), 6.98(1H,dd,J=1.9, 8.6 Hz), 7.34-7.50(7H,m), 7.65(1H,s), 7.70(1H,d,J=8.9Hz), 7.85(1H,s), 7.97(1H,s)

ESI (LC-MS positive mode) m/z 546 (M+H)

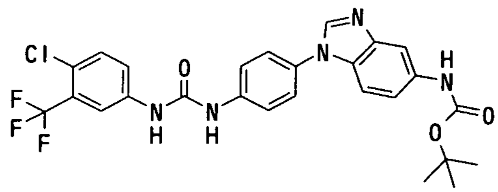
[Example 38]

(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido-

phenyl}-1H-benzimidazol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 38)

[0300]

[Formula 72]



[0301]

The title compound can be synthesized from 6-amino-1H-benzimidazole, di-tert-butyl dicarbonate, 4-fluoro-nitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by the same method as in Example 16.

[0302]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.50(9H,s), 7.37-7.50(2H,m), 7.55-7.70(6H,m), 7.88(1H,s), 8.12(1H,d,J=2.0 Hz), 8.42(1H,s), 9.11(1H,s), 9.25(1H,s), 9.34(1H,s)

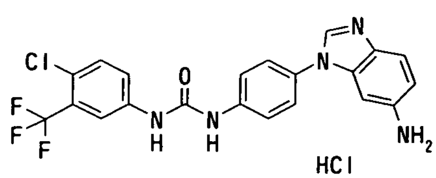
ESI (LC-MS positive mode) m/z 546 (M+H)

[Example 39]

1-[4-(6-Aminobenzimidazol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 39)

[0303]

[Formula 73]



[0304]

The title compound can be synthesized from (3-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)carbamic acid tert-butyl ester by the same method as in Example 17.

[0305]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.79(2H,br.s), 7.20-7.27(2H,m), 7.60-7.82(7H,m), 8.14(1H,s), 9.39(1H,s), 9.96(1H,s), 10.11(1H,s)

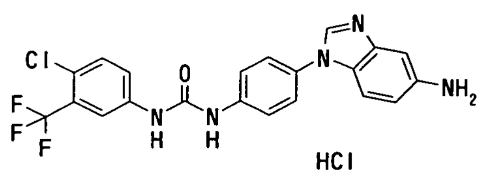
ESI (LC-MS positive mode) m/z 446 (M+H)

[Example 40]

1-[4-(6-Aminobenzimidazol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride (Table 1, Compound No. 40)

[0306]

[Formula 74]



[0307]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid tert-butyl ester by the same method as in Example 17.

[0308]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.23(1H,d,J=9.5 Hz), 7.52(1H,s), 7.63-7.77(7H,m), 8.13(1H,s), 9.32(1H,s), 9.85(1H,s), 10.00(1H,s)

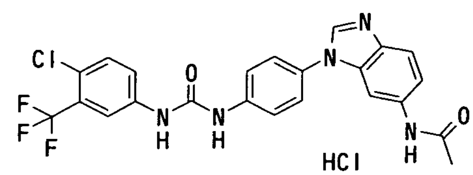
ESI (LC-MS positive mode) m/z 446 (M+H)

[Example 41]

N-(3-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-3H-benzimidazol-5-yl)acetamide (Table 1, Compound No. 41)

[0309]

[Formula 75]



[0310]

In a mixed solution of 2 mL of methylene chloride and 1 mL of pyridine, 40 mg (0.083 mmol) of 1-[4-(6-amino-benzimidazol-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)urea hydrochloride was dissolved, and 0.016 mL (0.16 mmol) of acetic anhydride was added thereto and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and the residue was distributed between ethyl acetate and a saturated ammonium chloride aqueous solution. The organic layer was washed with a saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue was triturated with n-hexane:ethyl acetate=1:2 to obtain 28 mg (70%) of N-(3-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-3H-benzimidazol-5-yl)acetamide (Table 1, Compound No. 41) as a white solid.

[0311]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.04(3H,s), 7.32 (1H,dd,J=1.6, 8.8 Hz), 7.55(2H,d,J=8.9 Hz), 7.62-

7.70(5H,m), 8.11(2H,dd,J=2.0, 8.9 Hz), 9.39(1H,s), 9.15(1H,s), 9.28(1H,s), 10.05(1H,s)

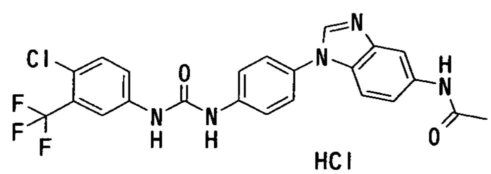
ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 42]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-benzimidazol-5-yl)acetamide (Table 1, Compound No. 42)

[0312]

[Formula 76]



[0313]

The title compound can be synthesized from 1-[4-[5-aminobenzimidazol-1-yl]phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride and acetic anhydride by the same method as in Example 41.

[0314]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.07(3H,s), 7.41-7.55(2H,m), 7.62-7.70(6H,m), 8.12(2H,dd,J=2.0, 5.9 Hz), 8.45(1H,s), 9.13(1H,s), 9.26(1H,s), 9.98(1H,s)

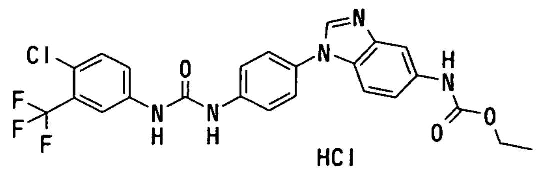
ESI (LC-MS positive mode) m/z 488 (M+H)

[Example 43]

(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid ethyl ester (Table 1, Compound No. 43)

[0315]

[Formula 77]



[0316]

The title compound can be synthesized from 1-[4-[5-aminobenzimidazol-1-yl]phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride and ethyl chloroformate by the same method as in Example 41.

[0317]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.27(3H,t,J=7.0 Hz), 4.15(2H,q,J=7.0 Hz), 7.41-7.70(7H,m), 7.91(1H,s), 8.11-8.13(2H,m), 8.45(1H,d,J=3.5 Hz), 9.13(1H,s), 9.25(1H,s), 9.63(0.5H,s), 9.99(0.5H,s)

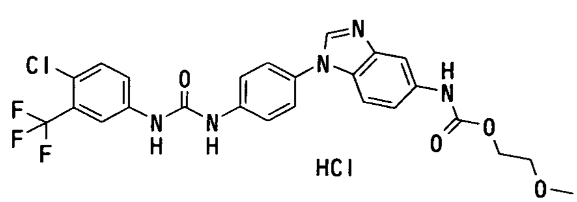
ESI (LC-MS positive mode) m/z 518 (M+H)

[Example 44]

(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-1H-benzimidazol-5-yl)carbamic acid 2-methoxyethyl ester (Table 1, Compound No. 44)

[0318]

[Formula 78]



[0319]

The title compound can be synthesized from 1-[4-(5-aminobenzimdazol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride and methoxyethyl

chloroformate by the same method as in Example 41.

[0320]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.27(3H,s), 3.57(2H,m), 4.22(2H,m), 7.41-7.70(7H,m), 7.92(1H,s), 8.11-8.13(2H,m), 8.45(1H,d,J=3.5 Hz), 9.13(1H,s), 9.26(1H,s), 9.76(0.5H,s), 9.99(0.5H,s)

ESI (LC-MS positive mode) m/z 548 (M+H)

[Example 45]

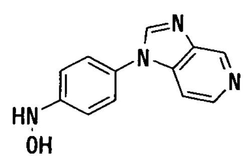
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-(4-imidazo[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 45)

Step A

Preparation of N-(4-imidazo[4,5-c]pyridin-1-yl-phenyl)hydroxylamine

[0321]

[Formula 79]



[0322]

In 3 mL of dioxane, 40 mg (0.167 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine obtained in Step A of Example 1 was dissolved, and 40 mg of zinc powder and 1 mL of a saturated ammonium chloride aqueous solution were added thereto and the mixture solution was vigorously stirred at room temperature for one hour. The reaction solution was distributed between ethyl acetate and water. The organic layer was washed with a sodium chloride

solution, dried and then concentrated under reduced pressure to obtain a crude product of N-(4-imidazo[4,5-c]pyridine-1-ylphenyl)-hydroxylamine. The product was used in the next reaction without further purification.

[0323]

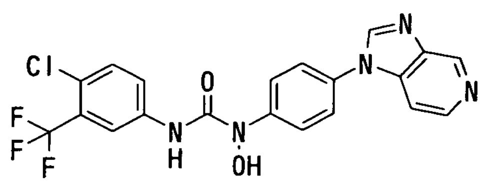
ESI (LC-MS positive mode) m/z 227 (M+H)

Step B

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxy-3-(4-imidazo[4,5-c]pyridin-1 ylphenyl)urea (Table 1, Compound No. 45)

[0324]

[Formula 80]



[0325]

In 5 mL of methylene chloride, 37 mg of N-(4-imidazo[4,5-c]pyridin-1-yl-phenyl)hydroxylamine obtained in Step A was dissolved, and 41 mg (1.84 mmol) of 4-chloro-3-(trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for three hours. The reaction solution was concentrated, and then the residue was distributed between ethyl acetate and a saturated ammonium chloride aqueous solution. The organic layer was washed with a saturated sodium chloride solution, dried and concentrated under reduced pressure. The residue was triturated with n-hexane:ethyl acetate=1:1 to obtain

12 mg (16%) of 1-(4-chloro-3-(trifluoromethyl) phenyl)-3-hydroxy-3-(4-imidazo-[4,5-c]pyridin-1-ylphenyl)urea (Table 1, Compound No. 45) as a white solid.

[0326]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.62-7.76(7H,m), 8.14-8.43(2H,m), 8.55(1H,m), 8.98(1H,m), 10.00(1H,s), 11.10(1H,s)

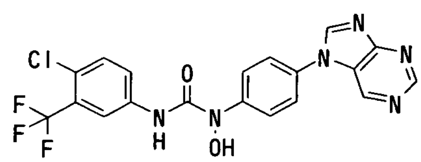
ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 46]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-(4-purin-7-ylphenyl)urea (Table 1, Compound No. 46)

[0327]

[Formula 81]



[0328]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0329]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(1H,d,J=10.9 Hz), 7.82(4H,dd,J=25.3, 13.0 Hz), 8.04(1H,dd,J=9.2, 3.7 Hz), 8.33(1H,d,J=2.3 Hz), 9.08(2H,d,J=6.8 Hz), 9.24(1H,s), 10.0(1H,s), 11.06(1H,s)

ESI (LC-MS positive mode) m/z 449 (M+H)

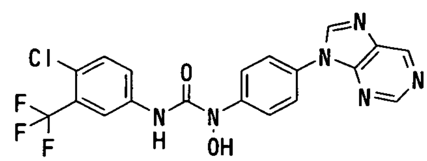
[Example 47]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-

(4-purin-9-ylphenyl)urea (Table 1, Compound No. 47)

[0330]

[Formula 82]



[0331]

The title compound can be synthesized from purine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0332]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.66(1H,d,J=8.9 Hz), 7.88(4H,dd,J=20.3, 12.8 Hz), 8.05(1H,dd,J=8.9, 2.3 Hz), 8.33(1H,d,J=2.3 Hz), 9.02(2H,d,J=1.3 Hz), 9.92(1H,s), 9.96(1H,s), 11.0(1H,s)

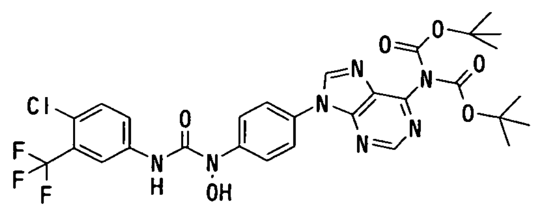
ESI (LC-MS positive mode) m/z 449 (M+H)

[Example 48]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-3-hydroxyurea (Table 1, Compound No. 48)

[0333]

[Formula 83]



[0334]

The title compound can be synthesized from 6-di-tert-

butoxycarbonylamino-9-(4-nitrophenyl)-9H-purine and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0335]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50(9H,s), 7.44(1H,d,J=8.6 Hz), 7.62(2H,d,J=7.0 Hz), 7.77(1H,dd,J=8.9, 3.0 Hz), 7.86(2H,d,J=7.2 Hz), 7.79(1H,d,J=2.7 Hz), 8.2(1H,s), 8.48(1H,d,J=4.3 Hz), 8.83(1H,s), 9.43(1H,br.s)

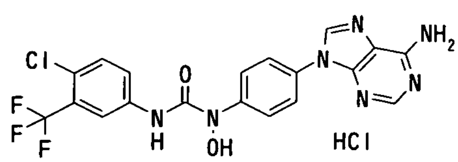
ESI (LC-MS positive mode)m/z 664(M+H)

[Example 49]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea hydrochloride (Table 1, Compound No. 49)

[0336]

[Formula 84]



[0337]

The title compound can be synthesized from 1-(4-chloro-3-(trifluoromethyl)phenyl-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-3-hydroxyurea by using the same techniques as in Example 30.

[0338]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(1H,d,J=8.9 Hz), 7.80(4H,dd,J=15.9, 9.3 Hz), 8.04(1H,dd,J=8.9, 2.3 Hz), 8.34(1H,d,J=3.6 Hz), 8.43(1H,s), 8.79(1H,s), 9.98(1H,s),

11.05(1H,s)

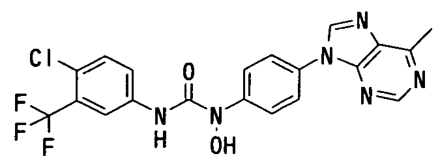
ESI (LC-MS positive mode) m/z 464 (M+H)

[Example 50]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-1-[4-(6-methylpurin-9-yl)phenyl]urea (Table 1, Compound No. 50)

[0339]

[Formula 85]



[0340]

The title compound can be synthesized from 6-methylpurine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0341]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.80(3H,s), 7.65(1H,d,J=8.9 Hz), 7.87(4H,dd,J=8.5, 7.6 Hz), 8.05(1H,dd,J=8.6, 2.6 Hz), 8.34(1H,d,J=2.6 Hz), 8.85(1H,s), 8.98(1H,s), 9.98(1H,s), 11.01(1H,s)

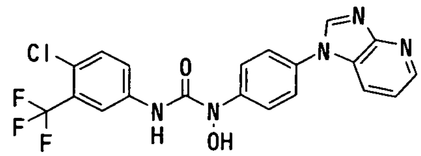
ESI (LC-MS positive mode) m/z 463 (M+H)

[Example 51]

3-(4-Chloro-3-trifluoromethyl)phenyl)-1-hydroxy-1-(4-imidazo[4,5-b]pyridin-1-ylphenyl)urea (Table 1, Compound No. 51)

[0342]

[Formula 86]



[0343]

The title compound can be synthesized from imidazo-[4,5-b]pyridine, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0344]

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.40(1H,dd,J=3.2 4.8 Hz), 7.66(1H,d,J=9.2 Hz), 7.83(2H,d,J=8.8 Hz, 7.93(2H,d,J=8.8 Hz), 8.06(1H,d,J=7.6 Hz), 8.22(1H,d,J=8.0 Hz), 8.35(1H,d,J=2.4 Hz), 8.45(1H,d,J=4.8 Hz), 8.90(1H, s), 9.98(1H,s), 10.99(1H,s)

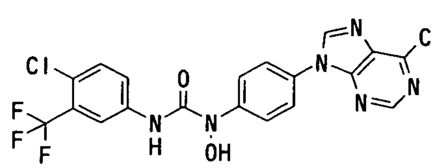
ESI (LC-MS positive mode)m/z 448 (M+H)

[Example 52]

1-[4-(6-Chloropurin-9-yl)phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-1-hydroxyurea (Table 1, Compound No. 52)

[0345]

[Formula 87]



[0346]

The title compound can be synthesized from 6-chloropurine, 4-fluoronitrobenzene and 4-chloro-3-

(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0347]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.65(1H,d,J=8.5 Hz), 7.88(4H,d), 8.04(1H,dd,J=8.5, 2.3 Hz), 8.32(1H,d,J=2.5 Hz), 8.85(1H,s), 9.12(1H, s), 10.01(1H,s), 11.03(1H,s)

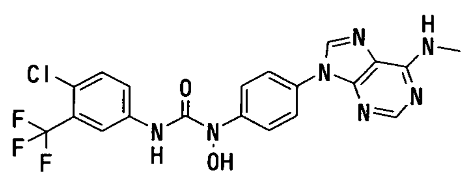
ESI (LC-MS positive mode) m/z 483 (M+H)

[Example 53]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-1-[4-(6-(methylamino)pruin-9-yl)phenyl]urea (Table 1, Compound No. 53)

[0348]

[Formula 88]



[0349]

In 2 mL of a 40% methylamine methanol solution, 30 mg (0.062 mmol) of 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea was dissolved and the solution stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure, and then the residue was purified by Megabond Elute Silica Gel (1 g, ethyl acetate:methanol= 10:1) to obtain 3.21 mg (11%) of 3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-1-[4-(6-(methylamino)pruin-9-yl)-phenyl]urea (Table 1, Compound No. 53)

[0350]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.15(3H,br.s), 7.67(1H,d,J=8.1 Hz), 7.82(4H,m), 8.06(1H,dd,J=8.2, 2.5 Hz), 8.28(1H,s), 8.35(1H,d,J=2.6 Hz), 8.56(1H,s), 9.96(1H,s), 10.98(1H,s)

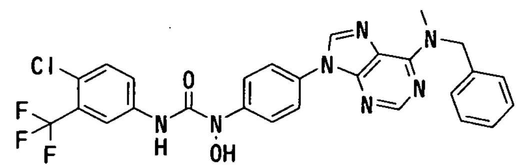
ESI (LC-MS positive mode) m/z 478 (M+H)

[Example 54]

1-{4-[6-(Benzyl-methylamino)purin-9-yl]phenyl}-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea (Table 1, Compound No. 54)

[0351]

[Formula 89]



[0352]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)-1-hdroxyurea and benzylmethylamine by using the same techniques as in Example 53.

[0353]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.27(3H,s), 7.26-7.32(5H,m), 7.38(1H,d,J=13.4 Hz), 7.42(2H,d,J=12.8 Hz), 7.54(1H,dd,J=13.4, 2.6 Hz), 7.65(2H,d,J=12.3 Hz), 7.80(1H,d,J=2.7 Hz), 7.89(1H, s), 8.15(1H,s), 8.39(1H,s)

ESI (LC-MS positive mode) m/z 568 (M+H)

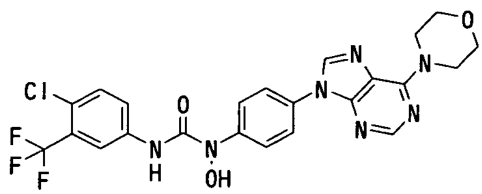
[Example 55]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-3-[4-(6-(morpholin-4-yl)purin-9-yl)phenyl]urea (Table 1,

Compound No. 55)

[0354]

[Formula 90]



[0355]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-1-hydroxyurea and morpholine by using the same techniques as in Example 53.

[0356]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.77(4H,t,J=4.8 Hz), 4.27(4H,br), 7.65(1H,d,J=8.9 Hz), 7.82(4H,s), 8.03(1H,dd,J=8.9, 2.6 Hz), 8.32(2H,d,J=2.5 Hz), 8.61(1H,s), 9.97(1H,s), 10.98(1H,s)

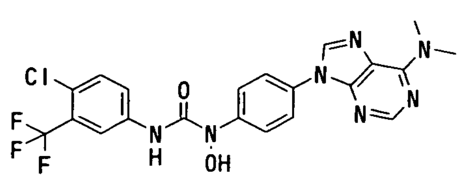
ESI (LC-MS positive mode) m/z 534 (M+H)

[Example 56]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-[4-(6-dimethylamino-purin-9-yl)phenyl]-1-hydroxyurea (Table 1, Compound No. 56)

[0357]

[Formula 91]



[0358]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)-1-hydroxyurea and dimethylamine by using the same techniques as in Example 53.

[0359]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.51(6H,br), 7.67(1H,d,J=8.1 Hz), 7.82(4H,m), 8.06(1H,dd,J=8.2, 2.5 Hz), 8.28(1H,s), 8.35(1H,d,J=2.6 Hz), 8.56(1H,s), 9.96(1H,s), 10.98(1H,s)

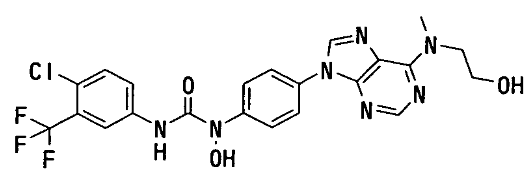
ESI (LC-MS positive mode) m/z 492 (M+H)

[Example 57]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-3-(4-{6-[(2-hydroxyethyl)-methylamine]purin-9-yl}-phenyl)urea (Table 1, Compound No. 57)

[0360]

[Formula 92]



[0361]

The title compound can be synthesized from 1-[4-(6-chloropurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl-phenyl)-1-hydroxyurea and 2-methylaminoethanol by using the same techniques as in Example 53.

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.71(2H,br), 4.80(1H,br), 7.66(1H,d,J=8.9 Hz), 7.82(4H,m), 8.05(1H,dd,J=8.9, 2.6 Hz), 8.27(1H,s), 8.33(1H,d,J=2.3 Hz), 8.56(1H,s), 9.97(1H,s), 10.99(1H,s)

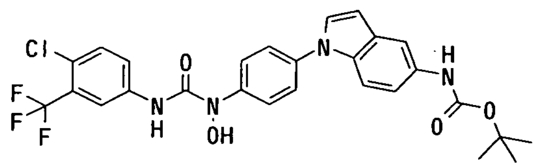
ESI (LC-MS positive mode) m/z 522 (M+H)

[Example 58]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 58)

[0362]

[Formula 93]



[0363]

The title compound can be synthesized from (1H-indol-5-yl)-carbamic acid tert-butyl ester, 4-fluoronitrobenzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 53.

[0364]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.56(9H,s), 6.57(2H,d,J=2.7 Hz), 6.88-7.01(2H,br), 7.15-7.70(9H,m), 7.83(1H,d,J=2.6 Hz), 8.18(1H,s), 8.37(1H,s)

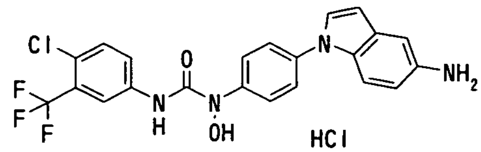
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 59]

1-[4-(5-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)1--hydroxyurea hydrochloride (Table 1, Compound No. 59)

[0365]

[Formula 94]



[0366]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]-phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 17.

[0367]

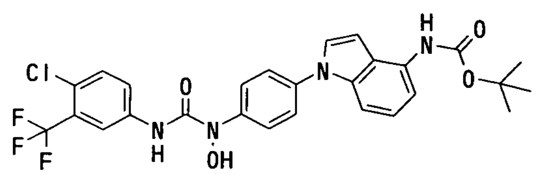
ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 60]

(1-{4-[3-(4-Chloro-3-(trifluormethyl)phenyl)-1-hydroxyureido]phenyl}-1H-indol-4-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 60)

[0368]

[Formula 95]



[0369]

The title compound can be synthesized from 4-aminoindole, di-tert-butyl dicarbonate, 4-fluoronitro-benzene and 4-chloro-3-(trifluoromethyl)phenyl isocyanate by using the same techniques as in Example 45.

[0370]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.55(9H,s), 6.52(1H,br), 6.71(1H,s), 7.04-7.56(6H,m), 7.65(1H,m), 7.88(1H,s), 8.17(1H, s), 8.30(1H,br)

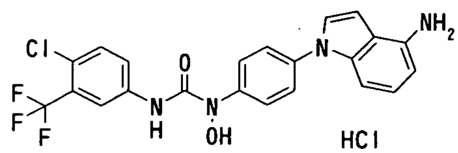
ESI (LC-MS positive mode) m/z 505 (M+H)

[Example 61]

1-[4-(4-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea hydrochloride (Table 1, Compound No. 61)

[0371]

[Formula 96]



[0372]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyureido]-phenyl}-1H-indol-4-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 17.

[0373]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.85(1H,d,J=3.2 Hz), 7.10(1H,d,J=7.6 Hz), 7.21(1H,t,J=8.3 Hz), 7.48(1H,d,J=8.5 Hz), 7.56(2H,d,J=8.5 Hz), 7.65(1H,d,J=8.2 Hz), 7.75(1H,d,J=3.3 Hz), 7.80(2H,d,J=8.5 Hz), 8.14(1H,dd,J=9.0, 2.8 Hz), 9.95(1H,s), 11.02(1H,br)

ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 62]

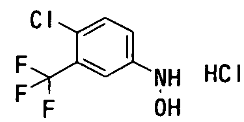
1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-1-hydroxyurea (Table 1, Compound No. 62)

Step A

Preparation of N-(4-chloro-3-(trifluoromethyl)-phenyl)hydroxylamine hydrochloride

[0374]

[Formula 97]



[0375]

In 21 mL of ethanol, 4.51 g (20 mmol) of 2-chloro-5-nitrobenzotrifluoride was dissolved, and a solution obtained by dissolving 3.8 g of zinc powder and 420 mg of ammonium chloride in 5 mL of water was added thereto, and the mixture solution was stirred at 70°C for one hour. The reaction solution after removal of insolubles by filtration was concentrated, and the residue was distributed between water and ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried, and then concentrated under reduced pressure, and to the obtained residue, 30 mL of a 4N hydrogen chloride ethyl acetate solution was added, and the formed white precipitate was collected by filtration, washed with ethyl acetate and vacuum dried to obtain 3.08 g (63%) of N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydro-chloride.

[0376]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.10(1H,dd,J=2.6, 8.5 Hz), 7.29(1H,d,J=2.6 Hz), 7.48(1H,d,J=8.5 Hz) 7.55(3H,br.s)

ESI (LC-MS positive mode) m/z 249 (M+H)

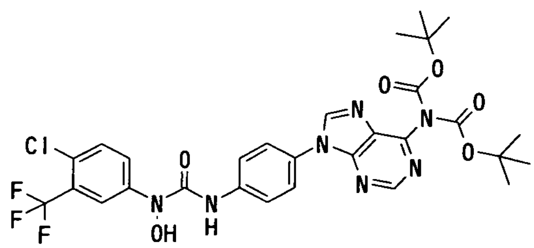
[0377]

Step B

Preparation of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-{4-[6-(di-tert-butoxycarbonylamino)purin-9-yl]phenyl}-1-hydroxyurea (Table 1, Compound No. 62)

[0378]

[Formula 98]



[0379]

In 6 mL of methylene chloride, 100 mg (2.35 mmol) of 9-(4-aminophenyl)-6-di-tert-butoxycarbonylamino-9H-purine prepared in Step B of Example 29 was dissolved, and 28 mg (0.94 mmol) of triphosgene was added thereto at one time. Successively, 0.042 mL (2.42 mmol) of Hunig's base was added thereto and the resulting solution was stirred at room temperature for five minutes. To the formed slurry, 64 mg (2.59 mmol) of N-(4-chloro-3-(trifluoromethyl)-phenyl)hydroxylamine hydrochloride dissolved in 0.123 mL of Hunig's base and 4 mL of methylene chloride was added dropwise and the resulting solution was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate (100 mL) and water

(100 mL), and the organic layer was washed with a saturated sodium chloride solution. The organic layer was dried and then concentrated under reduced pressure, and the residue was purified by Megabond Elute Silica Gel (5 g, n-hexane:ethyl acetate=1:1) to obtain 57 mg (37%) of 1-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxycarbonyl-amino)purin-9-yl]phenyl}-1-hydroxyurea (Table 1, Compound No. 62) as a white solid.

[0380]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50(18H,s), 6.80(1H,m), 7.39(1H,d,J=9.0 Hz), 7.48(1H,d,J=9.2 Hz), 7.62(4H,dd,J=26.1, 8.9 Hz), 7.82(1H,s), 8.03(1Hm), 8.15(1H,s), 8.22(1H,s), 8.28(1H,s), 8.74(1H,br), 8.88(1H,s)

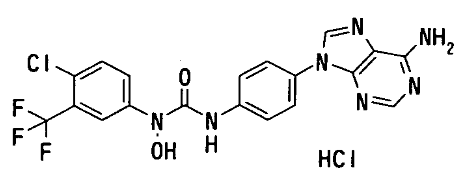
ESI (LC-MS positive mode) m/z 664 (M+H)

[Example 63]

1-[4-(6-Aminopurin-9-yl)phenyl]-3-(4-chloro-3-(tri-fluoromethyl)phenyl)-3-hydroxyurea hydrochloride (Table 1, Compound No. 63)

[0381]

[Formula 99]



[0382]

The title compound can be synthesized from (1-(4-chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-tert-butoxy-carbonylamino)purin-9-yl]phenyl}-1-hydroxyurea by using the

same techniques as in Example 30.

[0383]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.38(1H,d,J=8.6 Hz), 7.66-7.78(4H,m), 7.95(3H,d,J=6.9 Hz), 8.20(1H,d,J=2.7 Hz), 8.55(1H,d,J=2.6 Hz), 8.83(1H,d,J=4.3 Hz), 9.86(1H,s)

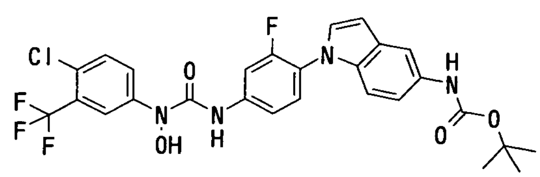
ESI (LC-MS positive mode) m/z 464 (M+H)

[Example 64]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 64)

[0384]

[Formula 100]



[0385]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride and [1-(4-amino-2-fluorophenyl)-1H-indol-5-yl]carbamic acid tert-butyl ester by using the same techniques as in Example 62.

[0386]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.52(9H,s), 6.60(1H,d,J=3.6 Hz), 7.08(1H,d,J=8.9 Hz), 7.22(1H,d,J=8.9 Hz), 7.44(1H,d,J=1.0 Hz), 7.55(1H,t,J=8.9 Hz), 7.68-7.78(3H,m), 7.85-7.95(2H,m) 8.18(1H,d,J=2.3 Hz), 9.19(1H,s), 10.00(1H,s),

11.19(1H,s)

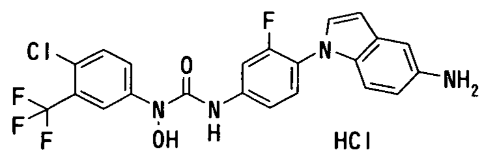
ESI (LC-MS positive mode) m/z 523.03 (M+H-t-Bu)

[Example 65]

3-[4-(5-Aminoindol-1-yl)-3-fluorophenyl]-1-(4-chloro-3-(trifluoromethyl)phenyl)-1-hydroxyurea (Table 1, Compound No. 65)

[0387]

[Formula 101]



[0388]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-ureido]-2-fluorophenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 30.

[0389]

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 6.81(1H,d,J=2.8 Hz), 7.16 (1H,d,J=2.4, 8.8 Hz), 7.32(1H,d,J=9.6 Hz), 7.55(1H,t,J=8.8 Hz), 7.67(2H,d,J=2.0 Hz), 7.73-7.76(2H,m), 7.93(2H,d,J=11.2 Hz), 8.19(1H,d,J=2.4 Hz), 10.04(1H,s), 10.09(2Hbr.s), 11.27(1H,s)

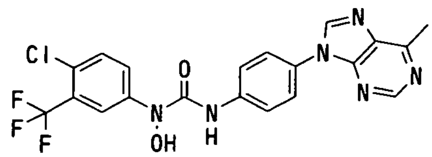
ESI (LC-MS positive mode) m/z 463.2 (M+H)

[Example 66]

3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-1-[4-(6-methylpurin-9-yl)phenyl]urea (Table 1, Compound No. 66)

[0390]

[Formula 102]



[0391]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 6-methylpurine and 4-fluoronitrobenzene by using the same techniques as in Example 62.

[0392]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.79(3H,s), 7.70(1H,d,J=8.9 Hz), 7.81-7.98(5H,m), 8.19(1H,d,J=2.7 Hz), 8.83(1H,s), 8.90(1H,s), 9.86(1H,s), 11.12(1H,s)

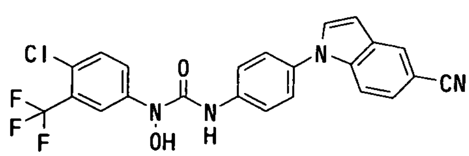
ESI (LC-MS positive mode) m/z 463 (M+H)

[Example 67]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-cyanoindol-1-yl)phenyl]-1-hydroxyurea (Table 1, Compound No. 67)

[0393]

[Formula 103]



[0394]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 5-cyanoindole and 4-fluoronitrobenzene by using the same techniques as in Example 62.

[0395]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.84(1H,d,J=3.3 Hz), 7.52-7.59(3H,m), 7.64(1H,d,J=8.9 Hz), 7.73(1H,d,J=8.9 Hz), 7.86(1H,d,J=3.3 Hz), 7.89-7.96(3H,m), 8.20(2H,m), 9.96(1H,s), 11.11(1H,s)

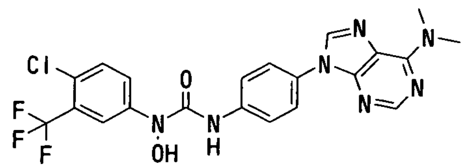
ESI (LC-MS positive mode) m/z 471.1 (M+H)

[Example 68]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(6-dimethylaminopurin-9-yl)phenyl]-3-hydroxyurea (Table 1, Compound No. 68)

[0396]

[Formula 104]



[0397]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride and [9-(4-aminophenyl)-9H-purin-6-yl]-dimethylamine by using the same techniques as in Example 62.

[0398]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 7.70(1H,d,J=9.2 Hz), 7.80(4H,dd,J=30.0, 8.9 Hz), 7.91(1H,dd,J=8.9, 2.6 Hz), 8.19(1H,d,J=2.7 Hz), 8.27(1H,s), 8.52(1H,s), 9.83(1H,s), 11.12(1H,s)

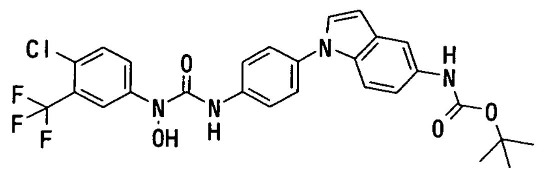
ESI (LC-MS positive mode) m/z 492 (M+H)

[Example 69]

(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester (Table 1, Compound No. 69)

[0399]

[Formula 105]



[0400]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, (1H-indol-5-yl)-carbamic acid tert-butyl ester and 4-fluoronitrobenzene by using the same techniques as in Example 62.

[0401]

^{1}H-NMR (270 MHz, $CDCl_3$) δ(ppm): 1.53(9H,s), 6.59(1H,d,J=3.3 Hz), 7.11(1H,dd,J=8.9, 2.3 Hz), 7.30(1H,d,J=3.3 Hz), 7.35-7.48(4H,m), 7.64(2H,d,J=6.6 Hz), 7.70(1H, br), 7.87(1H,dd, J=8.9, 2.7 Hz), 8.08(1H,d,J=2.7 Hz), 8.55(1H,s)

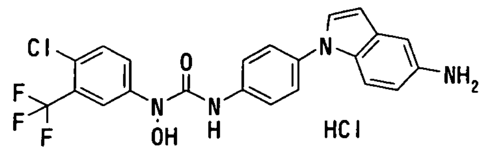
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 70]

(1-[4-(5-Aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride (Table 1, Compound No. 70)

[0402]

[Formula 106]



[0403]

The title compound can be synthesized from (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)carbamic acid tert-butyl ester by using the same techniques as in Example 30.

[0404]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.78(1H,d,J=3.3 Hz), 7.18(1H,dd,J=8.9, 2.4 Hz), 7.53(2H,d,J=8.9 Hz), 7.55-7.80(3H,m), 7.88(2H,d,J=9.8 Hz), 8.20(1H,d,J=2.7 Hz), 9.80(1H,s), 10.11(1H, br), 11.16(1H,s)

ESI (LC-MS positive mode) m/z 461 (M+H)

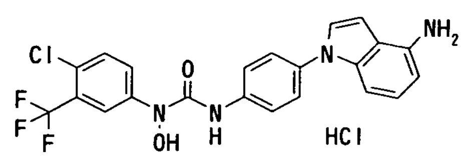
[Example 71]

1-[4-(4-Aminoindol-1yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride

(Table 1, Compound No. 71)

[0405]

[Formula 107]



[0406]

The titled compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 4-aminoindol, di-tert-butyl dicarbonate and 4-fluoronitrobenzene by using the same techniques as in

Example 70.

[0407]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 6.84(1H,d,J=3.3 Hz), 7.02(1H,d,J=7.5 Hz), 7.19(1H,t,J=7.6 Hz), 7.42(1H,d,J=7.9 Hz), 7.51(2H,d,J=8.9 Hz), 7.77-7.84(2H,m), 7.89(2H,d,J=8.9 Hz), 8.20(1H,d,J=2.6 Hz), 9.80(1H,s), 11.12(1H,s)

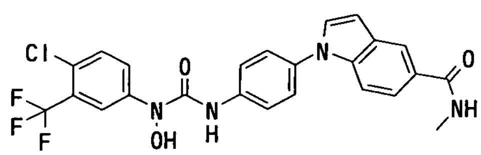
ESI (LC-MS positive mode) m/z 461 (M+H)

[Example 72]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indole-5-carboxylic acid methylamide (Table 1, Compound No. 72)

[0408]

[Formula 108]



[0409]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 1-(4-aminophenyl)-1H-indole-5-carboxylic acid methylamide by using the same techniques as in Example 62.

[0410]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.82(3H,d,J=4.3 Hz), 6.80(1H,d,J=3.3 Hz), 7.53-7.58(3H,m), 7.68-7.74(3H,m), 7.85-7.93(3H,m), 8.20(2H,m), 8.37(1H,q,J=4.3 Hz), 9.83(1H,s), 11.12(1H,s)

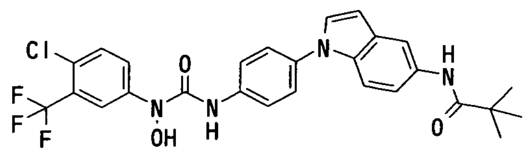
ESI (LC-MS positive mode) m/z 503.5 (M+H)

[Example 73]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-2,2-dimethylpropionamide (Table 1, Compound No. 73)

[0411]

[Formula 109]



[0412]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and pivalic anhydride by using the same techniques as in Example 41.

[0413]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.23(9H,s), 6.62(1H,d,J=3.3 Hz), 7.34(1H,d,J=8.9 Hz), 7.46(1H,d,J=8.9 Hz), 7.50(2H,d,J=8.9 Hz), 7.56(1H,d,J=3.3 Hz), 7.72(1H,d,J=8.9 Hz), 7.87(2H,d,J=8.9 Hz), 7.90-7.96(2H,m), 8.20(1H,d,J=2.3 Hz), 9.12(1H,s), 9.78(1H,s), 11.09 (1H,s)

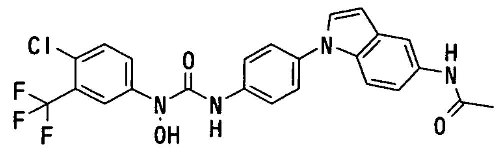
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 74]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)acetamide (Table 1, Compound No. 74)

[0414]

[Formula 110]



[0415]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and acetic anhydride by using the same techniques as in Example 41.

[0416]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 2.04(3H,s), 6.62(1H,d,J=4.3 Hz), 7.27(1H,dd,J=9.3, 2.0 Hz), 7.35-7.65(4H,m), 7.70(1H,d,J=8.9 Hz), 7.83(2H,d,J=9.0 Hz), 7.94(1H,dd,J=9.2, 2.7 Hz), 7.97(1H,s), 8.20(1H,d,J=2.7 Hz), 9.78(1H,s), 9.86(1H,s), 11.09(1H,s)

ESI (LC-MS positive mode) m/z 503 (M+H)

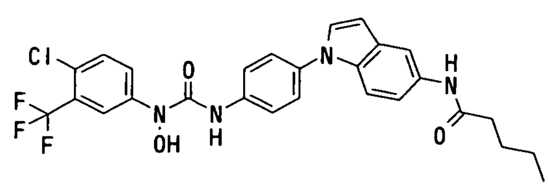
[Example 75]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)pentanamide

(Table 1, Compound No. 75)

[0417]

[Formula 111]



[0418]

The title compound can be synthesized from 1-[4-(5-

aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-valeroyl chloride by using the same techniques as in Example 41.

[0419]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.90(3H,q,J=5.1 Hz), 1.31(2H,m), 1.61(2H,m), 2.31(1H,t,J=6.5 Hz), 2.76(1H,t,J=5.5 Hz), 6.62(1H,d,J=3.3 Hz), 7.29(1H,dd,J=8.9, 2.0 Hz), 7.46(1H,d,J=8.9 Hz), 7.55(2H,d,J=8.9 Hz), 7.58(1H,d,J=3.3 Hz), 7.70(2H,d,J=8.9 Hz), 7.74(1H,d,J=2.1 Hz), 7.78(1H,d,J=8.9 Hz), 7.94(1H,d,J=2.6 Hz), 8.00(1H,d,J=2.6 Hz), 9.65(1H,s), 9.77(1H,s)

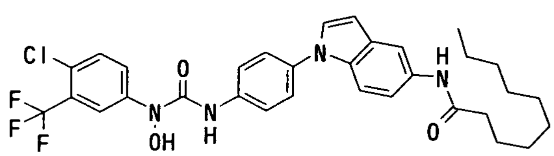
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 76]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)decanamide (Table 1, Compound No. 76)

[0420]

[Formula 112]



[0421]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-decanoyl chloride by using the same techniques as in Example 41.

[0422]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 0.89(3H,t,J=6.3 Hz), 1.27(14H,br), 2.32(2H,d,J=8.0 Hz), 6.61(1H,d,J=3.3 Hz), 7.06-7.31(5H,m), 7.35-7.50(3H,m), 7.71(1H,d,J=2.3 Hz), 7.75(1H,s), 7.78(1H,d,J=2.7 Hz), 9.81(1H,br)

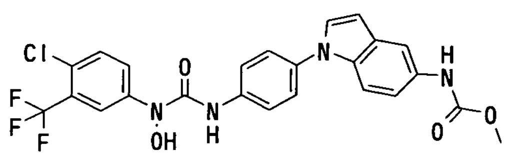
ESI (LC-MS positive mode) m/z 615 (M+H)

[Example 77]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid methyl ester (Table 1, Compound No. 77)

[0423]

[Formula 113]



[0424]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and methyl chloroformate by using the same techniques as in Example 41.

[0425]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 3.71(3H,s), 6.60(1H,d,J=3.0 Hz), 6.75(1H,s), 7.04(1H,d,J=8.9 Hz), 7.15-7.30(5H,m), 7.36(1H,d,J=8.9 Hz), 7.51(1H,s), 7.68-7.72(2H,m), 7.93(1H,d,J=2.6 Hz), 8.93(1H,br)

ESI (LC-MS positive mode) m/z 519 (M+H)

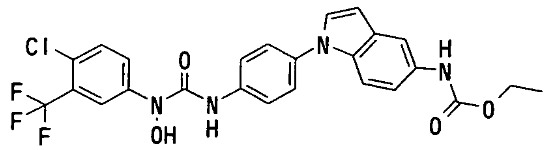
[Example 78]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-

hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid ethyl ester (Table 1, Compound No. 78)

[0426]

[Formula 114]



[0427]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and ethyl chloroformate by using the same techniques as in Example 41.

[0428]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.23(3H,t,J=7.1 Hz), 4.14(2H,q,J=7.2 Hz), 6.62(1H,d,J=2.6 Hz), 6.63(1H,s), 7.09(1H,dd,J=8.9, 2.0 Hz), 7.25-7.45(6H,m), 7.53(1H,d,J=2.0 Hz), 7.75(1H,dd,J=8.2, 2.3 Hz), 7.95(1H,d,J=2.6 Hz)

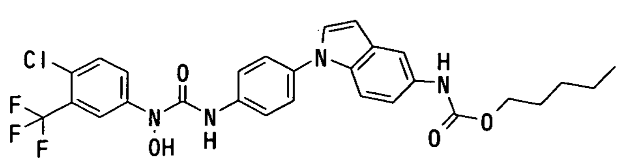
ESI (LC-MS positive mode) m/z 533 (M+H)

[Example 79]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid pentyl ester (Table 1, Compound No. 79)

[0429]

[Formula 115]



[0430]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-pentyl chloroformate by using the same techniques as in Example 41.

[0431]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 0.91(3H,t,J=6.6 Hz), 1.32(4H,m), 1.62(2H,m), 4.03(2H,t,J=6.6 Hz), 6.61(1H,d,J=2.6 Hz), 6.70(1H,s), 7.07(1H,dd,J=8.5, 2.0 Hz), 7.16-7.35(6H,m), 7.37(1H,d,J=8.9 Hz), 7.51(1H,d,J=2.0 Hz), 7.72(1H,br), 7.75(1H,s), 7.95(1H,s)

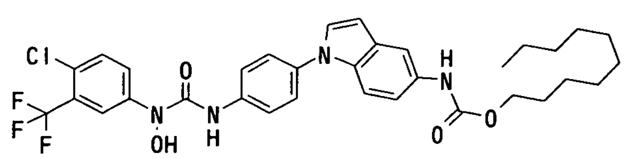
ESI (LC-MS positive mode) m/z 557 (M+H)

[Example 80]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid decyl ester (Table 1, Compound No. 80)

[0432]

[Formula 116]



[0433]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and n-decyl chloroformate by using the same techniques as in Example 41.

[0434]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 0.89(3H,m), 1.30(14H,br),

1.61(2H,m), 4.03(2H,t,J=7.0 Hz), 6.60(1H,d,J=3.3 Hz), 6.68(1H,s), 6.76(1H,d,J=8.9 Hz), 7.07(1H,dd,J=9.0, 2.0 Hz), 7.17-7.36(6H,m), 7.38(1H,d,J=8.8 Hz), 7.52(1H,d,J=2.0 Hz), 7.66-7.75(2H,m), 7.95(1H,d,J=2.7 Hz), 8.92(1H,br)

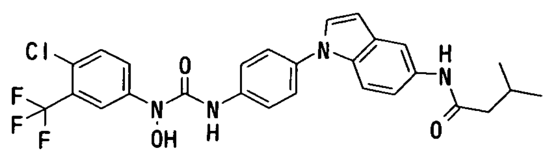
ESI (LC-MS positive mode) m/z 645 (M+H)

[Example 81]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3-methylbutyl-amide (Table 1, Compound No. 81)

[0435]

[Formula 117]



[0436]

The titled compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and isovaleroyl chloride by using the same techniques as in Example 41.

[0437]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.95(6H,d,J=6.3 Hz), 2.12(1H,m), 2.21(2H,m), 6.62(1H,d,J=2.3 Hz), 7.29(1H,d,J=8.9 Hz), 7.45-7.95(7H,m), 8.00(1H,d,J=2.0 Hz), 8.19(1H,d,J=2.7 Hz), 9.75(2H,d,J=5.9 Hz), 11.08(1H,s),

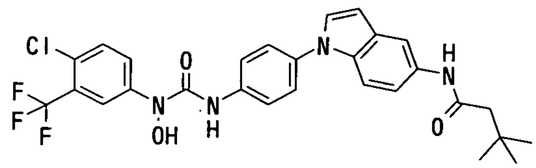
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 82]

N-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3,3-dimethyl-butylamide (Table 1, Compound No. 82)

[0438]

[Formula 118]



[0439]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and tert-butylacetyl chloride by using the same techniques as in Example 41.

[0440]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.03(9H,s), 2.20(2H,s), 6.62(1H,d,J=3.2 Hz), 7.27(1H,d,J=10.8 Hz), 7.45(1H,d,J=8.9 Hz), 7.51(2H,d,J=8.9 Hz), 7.59(1H,d,J=8.9 Hz), 7.72(1H,d,J=9.2 Hz), 7.85(2H,d,J=8.9 Hz), 7.93(1H,d,J=11.3 Hz), 8.00(1H,s), 8.19(1H,d,J=2.4 Hz), 9.69(1H,s), 9.78(1H,s), 11.09(1H,s),

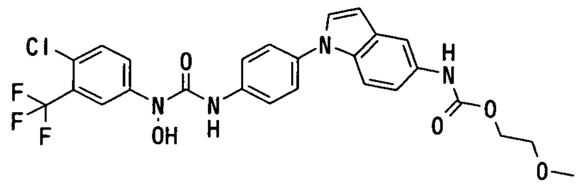
ESI (LC-MS positive mode) m/z 559 (M+H)

[Example 83]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)carbamic acid 2-methoxyethyl ester (Table 1, Compound No. 83)

[0441]

[Formula 119]



[0442]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and 2-methoxyethyl chloroformate by using the same techniques as in Example 41.

[0443]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.28(3H,s), 3.57(2H,t,J=5.0 Hz), 4.21(2H,t,J=5.0 Hz), 6.60(1H,d,J=3.3 Hz), 7.25(1H,d,J=8.6 Hz), 7.45(1H,d,J=8.9 Hz), 7.52(2H,d,J=8.9 Hz), 7.58(1H,d,J=3.3 Hz), 7.70(1H,d,J=8.6 Hz), 7.78(1H,br), 7.85(2H,d,J=8.9 Hz), 7.91(1H,dd,J=8.9, 2.3 Hz), 8.20(1H,d,J=2.6 Hz), 9.58(1H,br), 9.75(1H,s), 11.10(1H,s),

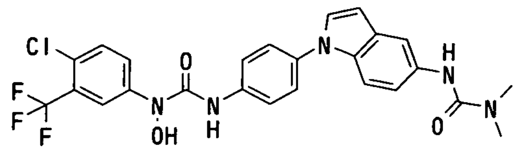
ESI (LC-MS positive mode) m/z 563 (M+H)

[Example 84]

3-(1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-1,1-dimethylurea (Table 1, Compound No. 84)

[0444]

[Formula 120]



[0445]

The title compound can be synthesized from 1-[4-(5-aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and N,N-dimethyl-carbamic acid chloride by using the same techniques as in Example 41.

[0446]

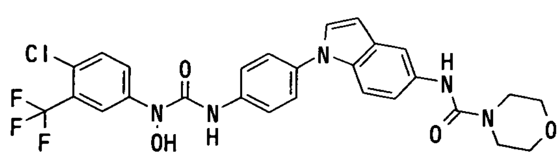
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.92(3H,s), 3.16(3H,s), 4.66(1H,br), 6.38(1H,d,J=3.0 Hz), 6.56(2H,dd,J=8.6, 2.0 Hz), 6.76(1H,d,J=2.0 Hz), 7.26(1H,d,J=8.6 Hz), 7.43(1H,d,J=3.3 Hz), 7.50(2H,d,J=8.9 Hz), 7.65(2H,d,J=8.9 Hz), 7.75(1H,d,J=8.9 Hz), 7.99(1H,d,J=2.3 Hz), 9.55(1H,s) ESI (LC-MS positive mode) m/z 532 (M+H)

[Example 85]

Morpholine-4-carboxylic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 85)

[0447]

[Formula 121]



[0448]

The title compound can be synthesized from 1-[4-(5-

aminoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-pheny)-3-hydroxyurea hydrochloride and 4-morpholinyl-carbamic acid chloride by using the same techniques as in Example 41.

[0449]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 3.41(4H,m), 3.63(4H,m), 6.58(1H,d,J=2.1 Hz), 7.22(1H,d,J=8.9 Hz), 7.40-7.78(6H,m), 7.85(2H,d,J=8.9 Hz), 7.96(1H,d,J=8.9 Hz), 8.19(1H,d,J=2.0 Hz), 8.45(1H,s), 9.78(1H,s), 11.08(1H,s)

ESI (LC-MS positive mode) m/z 574 (M+H)

[Example 86]

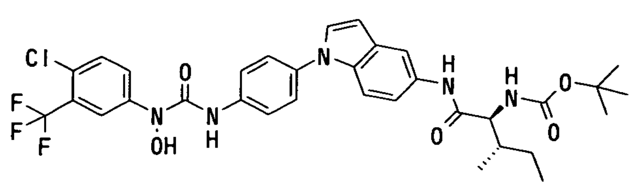
(2S,3S)-2-Amino-3-methylpentanoic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 86)

Step A

Preparation of [1-(1-{4-[3-(4-chloro-3-(trifluoro-methyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-ylcarbamoyl)-(2S,3S)-2-methylbutyl]carbamic acid tert-butyl ester

[0450]

[Formula 122]



[0451]

In a mixed solution of 0.2 mL of methanol and 2.0 mL

of methylene chloride, 80 mg (0.16 mmol) of 1-[4-(5-amino-indol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyurea hydrochloride was dissolved, and 59 mg (0.18 mmol) of tert-butyoxycarbonyl-L-isoleucine N-hydroxy-succinimide ester and 0.5 mL of pyridine were added thereto and the mixture solution was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution. The orgnic layer was dried and then concentrated under reduced pressure, and the residue was purified by Megabond Elute Silica Gel (2 g, n-hexane:ethyl acetate=1:1) to obtain 15.0 mg (14%) of [1-(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]-phenyl}-1H-indol-5-ylcarbamoyl)-(2S,3S)-2-methylbutyl]-carbamic acid tert-butyl ester as a white solid.

[0452]

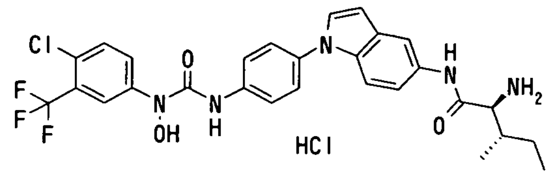
ESI (LC-MS positive mode) m/z 674 (M+H)

Step B

Preparation of (2S,3S)-2-amino-3-methylpentanoic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 86)

[0453]

[Formula 123]



[0454]

In 2 mL of a 4N hydrogen chloride ethyl acetate solution, 15.0 mg (14%) of [1-(1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-ylcarbamoyl)-(2S,3S)-2-methylbutyl]carbamic acid tert-butyl ester was dissolved and the solution was stirred under cooling with ice for one hour. The reaction solution was concentrated under reduced pressure, and then the residue was triturated with diethyl ether to obtain 7.0 mg (17%) of (2S,3S)-2-amino-3-methylpentanic acid (1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)-3-hydroxy-ureido]phenyl}-1H-indol-5-yl)amide (Table 1, Compound No. 86) as a white solid.

[0455]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.85-1.03(6H,m), 1.63(1H,m), 1.95(1H,br), 3.85(1H,br), 6.68(1H,d,J=3.3 Hz), 7.32-7.95(8H,m), 8.21(1H,m), 9.73(1H,d,J=6.9 Hz), 10.53(1H,br), 11.19(1H,d,J=3.3 Hz)

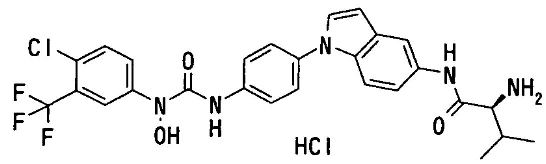
ESI (LC-MS positive mode) m/z 574 (M+H)

[Example 87]

(S)-2-Amino-N-(1-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyureido]phenyl}-1H-indol-5-yl)-3-methylbutylamide (Table 1, Compound No. 87)

[0456]

[Formula 124]



[0457]

The title compound can be synthesized from 1-[4-(5-amonoindol-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)-3-hydroxyurea hydrochloride and tert-butoxy-carbonyl-L-valine N-hydroxysuccinimide ester by using the same techniques as in Example 86.

[0458]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.02(6H,d,J=7.0 Hz), 2.22(1H,m), 3.83(1H,br), 6.69(1H,d,J=3.3 Hz), 7.40(1H,dd,J=8.9, 2.0 Hz), 7.68(1H,d,J=8.9 Hz), 7.75-7.95(7H,m), 8.20(1H,s), 8.27(2H,br), 9.75(1H,br), 10.55(1H,br), 11.17(1H,br)

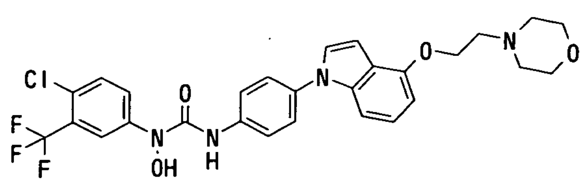
ESI (LC-MS positive mode) m/z 560 (M+H)

[Example 88]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-1-hydroxy-3-{4-[4-(2-(morpholin-4-yl)ethoxy)indol-1-yl]phenyl}-urea (Table 1, compound No. 88)

[0459]

[Formula 125]



[0460]

The title compound can be synthesized from N-(4-chloro-3-(trifluoromethyl)phenyl)hydroxylamine hydrochloride, 1H-indole-4-ol, 2-(morpholin-4-yl)ethanol and 4-fluoronitrobenzene in the same manner as in Example 62.

[0461]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 2.55(4H,br), 2.80(2H,t,J=5.4 Hz), 3.60(4H,t,J=4.6 Hz), 4.25(2H,t,J=5.7 Hz), 6.66(2H,m), 7.11(2H,m), 7.50(3H,m), 7.70(1H,d,J=8.9 Hz), 7.86(2H,d,J=8.9 Hz), 8.20(1H,d,J=2.7 Hz), 9.79(1H,s), 11.10(1H,s)

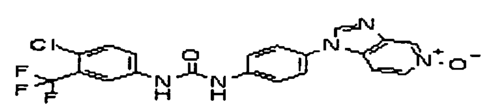
ESI (LC-MS positive mode) m/z 575 (M+H)

[Example 89]

Synthesis of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea (Table 1, Compound No. 89)

[0462]

[Formula 126]



[0463]

In 10 mL of acetic acid, 540 mg (1.25 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-imidazo[4,5-c]-pyridin-1-yl)urea prepared in Example 1 was dissolved, and 3 mL of a 30% hydrogen peroxide aqueous solution was added thereto and the mixture solution was stirred at 50°C for one day. The solvent was distilled under reduced pressure, and the residue was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm,

dichloromethane:methanol=9:1 to 4:1) to obtain 282 mg (53%) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea (Table 1, Compound No. 89) as a white solid.

[0464]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 7.60-7.78(7H,m), 8.13-8.15(2H,m), 8.77(1H,s), 8.83(1H,d,J=1.3 Hz), 9.20(1H,s), 9.29(1H,s)

ESI (LC-MS positive mode) m/z 448 (M+H)

[Example 90]

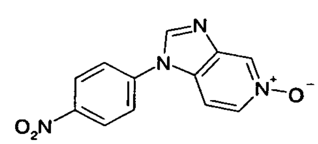
Synthesis of 1-[4-(4-chloro-imidazo[4,5-c]pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (Table 1, Compound No. 90)

Step A

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-pyridine 5-oxide

[0465]

[Formula 127]



[0466]

In 15 mL of acetic acid, 483 mg (2.01 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine prepared in Step A of Example 1 was dissolved, and 2 mL of a 30% hydrogen peroxide aqueous solution was added thereto and the mixture solution was stirred at 50°C for 14 hours. The solvent was distilled under reduced pressure, and the obtained residue

was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol=9:1) to obtain 298 mg (57%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine 5-oxide as a pale yellow solid.

[0467]

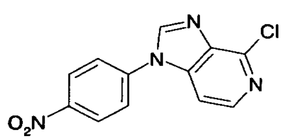
^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.80 (1H,dd,J=0.6, 7.2 Hz), 8.05(2H,m), 8.20(1H,dd,J=1.7, 7.0 Hz), 8.45(2H,m), 8.87(1H,s), 8.97(1H,s)

Step B

Preparation of 4-chloro-1-(4-nitrophenyl)-1H-imidazo-[4,5-c]pyridine

[0468]

[Formula 128]



[0469]

In 5 mL of phosphorus oxychloride, 42 mg (0.164 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine 5-oxide was dissolved and the solution was stirred at 80°C for 14 hours. Excess reagent was distilled under reduced pressure, and the residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogencarbonate aqueous solution (10 mL). The combined organic layers were washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was separated by a silica gel column

(Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol=19:1) to obtain 45 mg (quantitative) of 4-chloro-1-(4-nitrophenyl)-1H-imidazo-[4,5-c]pyridine as a pale yellow solid.

[0470]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 7.48 (1H,d,J=5.6 Hz), 8.05(2H,m), 7.70-7.80(3H,m), 8.30(1H,s), 8.36(1H,d,J=5.6 Hz), 8.56(2H,m)

ESI (LC-MS positive mode) m/z 275 (M+H)

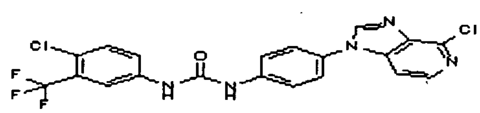
[0471]

Step C

Preparation of 1-[4-(4-chloro-imidazo[4,5-c]pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl) urea (Table 1, Compound No. 90)

[0472]

[Formula 129]



[0473]

In 50% acetic acid, 41 mg (0.150 mmol) of 4-chloro-1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine prepared in Step B was dissolved, and 42 mg (0.75 mmol) of iron powder was added thereto, and the mixture solution was stirred at 50°C for one hour. The solvent was distilled, and the obtained residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogencarbonate aqueous solution (10 mL). The combined organic layers were washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate, and

then concentrated under reduced pressure to obtain 1-(4-aminophenyl)-4-chloroimdazo-1H-[4,5-c]pyridine as a crude product. In 10 mL of dichloromethane, the crude product without further purification was dissolved, and 31 mg (0.15 mmol) of 4-chloro-3-trifluoromethyl)phenyl isocyanate was added thereto and the mixture solution was stirred at room temperature for two hours. The solvent was distilled under reduced pressure, and the obtained residue was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane: methanol=19:1), and the obtained crude product was recrystallized from methanol to obtain 44 mg (63%) of 1-[4-(4-chloro-imidazo[4,5-c]pyridin-1-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (Table 1, Compound No. 90) as a colorless crystal.

[0474]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 7.60-7.67(5H,m), 7.70-7.75(2H,m), 8.14(1H,d,J=2.0 Hz), 8.23(1H,d,J=5.6 Hz), 8.79(1H,s), 9.19(1H,s), 9.29(1H,s)

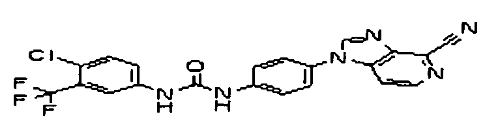
ESI (LC-MS positive mode) m/z 467 (M+H)

[Example 91]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-cyanoimidazo[4,5-c]pyridin-1-yl)phenyl]urea (Table 1, Compound No. 91)

[0475]

[Formula 130]



[0476]

In 10 mL of acetonitrile, 112 mg (0.25 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(5-oxy-imidazo[4,5-c]pyridin-1-yl)phenyl]urea prepared in Example 89 was dissolved, and 104 μL (0.75 mmol) of trimethylsilylcyanide and 20 μl (0.75 mmol) of 1,8-diazabicyclo[5.4.0]undecene were added thereto and the mixture solution was stirred at 80°C for six hours. The solvent was distilled under reduced pressure, and the residue was separated by a silica gel column (Si-10, a product of Kusano Co., Ltd., column 30 cm, dichloromethane:methanol=9:1 to 4:1) to obtain 15 mg (15%) of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-[4-(4-cyanoimidazo[4,5-c]pyridin-1-yl)phenyl]- urea (Table 1, Compound No. 91) as a white solid.

[0477]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 7.62-7.67(4H,m), 7.70-7.75(2H,m), 7.98(1H,d,J=7.3 Hz), 8.13(1H,d,J=2.3 Hz), 8.59(1H,d,J=5.6 Hz), 8.99(1H,s), 9.19(1H,s), 9.29(1H,s)

ESI (LC-MS positive mode) m/z 457 (M+H)

[Example 92]

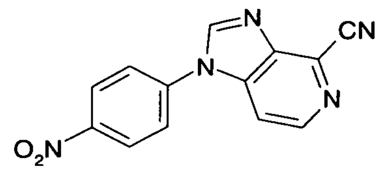
1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide (Table 1, Compound No. 92)

Step A

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-pyridine-4-carbonitrile

[0478]

[Formula 131]



[0479]

In a mixed solvent of 1 mL of dimethylformamide and 2mL of dioxane, 100 mg (0.39 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine 5-oxide prepared in Step A of Example 90 was dissolved, and 310 μL (0.78 mmol) of tri-methylsilylcyanide and 144 μL (0.78 mmol) of N,N-dimethylcarbamoyl chloride were added thereto and the mixture solution was stirred at 90°C for 14 hours. The solvent was distilled, and the residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogen-carbonate aqueous solution (10 mL). The combined organic layers was washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was triturated with ethyl acetate to obtain 78 mg (75%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carbonitrile as a pale yellow solid.

[0480]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 8.07-8.13(2H,m), 8.14-8.16(1H,m), 8.47-8.53(2H,m), 8.67(1H,d,J=5.5 Hz), 9.20(1H,s)

ESI (LC-MS positive mode) m/z 266 (M+H)

[0481]

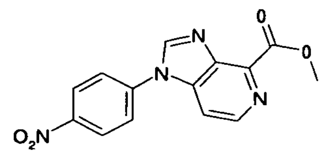
Step B

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-

pyridine-4-carboxylic acid methyl ester

[0482]

[Formula 132]



[0483]

In 10 mL of methanol, 74 mg (0.28 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carbonitrile prepared in Step A was dissolved, and 2 mL of a 4N hydrogen chloride dioxane solution was added thereto, and the mixture solution was refluxed under heating with stirring for four hours. The solvent was distilled under reduced pressure, and the residue was distributed between ethyl acetate (10 mL×2) and a sodium hydrogencarbonate aqueous solution (10 mL). The combined organic layers was washed with a saturated sodium chloride solution, dried on anhydrous sodium sulfate and then concentrated under reduced pressure. The solvent was distilled and the residue was separated by Megabond Elute Silica Gel (2 g, dichloromethane:methanol=30:1) to obtain 34 mg (41%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-5-carboxylic acid methyl ester as a white solid.

[0484]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 4.17(3H,s), 7.70-7.80(3H,m), 8.40(1H,s), 8.52-8.57(2H,m), 8.72-8.74(1H,d,J=6.3 Hz)

ESI (LC-MS positive mode) m/z 299 (M+H)

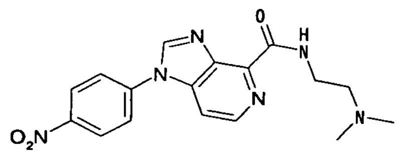
[0485]

Step C

Preparation of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]-pyridine-4-carboxylic acid (2-(dimethylamino)ethyl amide

[0486]

[Formula 133]



[0487]

In 5 mL of methanol, 11 mg (0.037 mmol) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methyl ester prepared in Step B was dissolved, and 100 μL of N,N-dimethylethylenediamine was added thereto and the solution was refluxed under heating with stirring for two hours. The solvent was distilled under reduced pressure, and the residue was separated by Megabond Elute Silica Gel (1 g, dichloromethane:nethanol=30:1 to 4:1) to obtain 7.3 mg (51%) of 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide as a white solid.

[0488]

^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 2.30(6H,s), 2.65(2H,t,J=6.3 Hz), 3.73(2H,t,J=5.9 Hz), 7.62(1H,d, J=5.3 Hz), 7.73-7.77(2H,m), 8.39(1H,s), 8.50-8.54(2H,m), 8.64(1H,d,J=5.6 Hz), 8.90(1H,br.s)

ESI (LC-MS positive mode) m/z 355 (M+H)

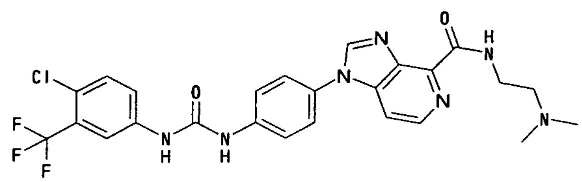
[0489]

Step D

Preparation of 1-{4-[3-(4chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide (Table 1, Compound No. 92)

[0490]

[Formula 134]



[0491]

The title compound can be synthesized from 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid (2-(dimethylamino)ethyl)amide and 4-chloro-3-(trifluoro-methyl)phenyl isocyanate in the same manner as in Steps B and C of Example 1.

[0492]

^{1}H-NMR (270 MHz, CD_3OD) δ(ppm): 2.39(6H,s), 2.73(2H,t,J=6.6 Hz), 3.73(2H,t,J=6.6 Hz), 7.50-7.70(4H,m), 7.73-7.77(3H,m), 8.04(1H,m), 8.54(1H,m), 8.66(1H,s)

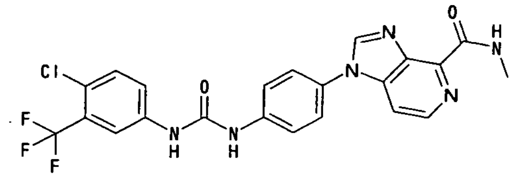
ESI (LC-MS positive mode) m/z 546 (M+H)

[Example 93]

1-{4-[3-(4-Chloro-3-(trimethylfluoro)phenyl)ureido]-phenyl}-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methylamide (Table 1, Compound No. 93)

[0493]

[Formula 135]



[0494]

The title compound can be synthesized from 1-(4-nitrophenyl)-1H-imidazo[4,5-c]pyridine-4-carboxylic acid methyl ester, methylamine and 4-chloro-3-(trifluoromethyl)phenyl isocyanate in the same manner as in Steps C and D of Example 92.

[0495]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.39(3H,d,J=4.6 Hz), 7.62-7.80(7H,m), 8.14(1H,d,J=2.0 Hz), 8.49(1H,d,J=5.6 Hz), 8.83(1H,s), 9.02(1H,br.q,J=4.6 Hz), 9.21(1H,s), 9.30(1H,s)

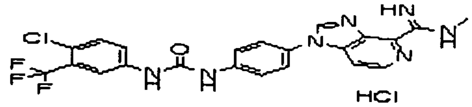
ESI (LC-MS positive mode) m/z 489 (M+H)

[Example 94]

1-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-N-methyl-1H-imidazo[4,5-c]pyridine-4-carboxamidine hydrochloride (Table 1, Compound No. 94)

[0496]

[Formula 136]



[0497]

In 5 mL of methanol, 12 mg (0.026 mmol) of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-[4-(4-cyanoimidazo-

[4,5-c]pyridin-1-yl)phenyl]urea prepared in Example 91 was dissolved, and one drop (a catalytic amount) of a 28% methanol solution of sodium methylate was added thereto and the solution was stirred at room temperature for six hours. The reaction solution was neutralized with one drop of acetic acid, and then 50 μL of a dimethylamine 40% methanol solution was added thereto and the mixture solution was further stirred at room temperature for 14 hours. The solvent was distilled under reduced pressure, and the residue was separated by reversed phase high-pressure liquid chromatography (C18 Column, acetonitrile:water=55:45, 0.05% trifluoroacetic acid). The fraction containing a target product was concentrated, and then trifluoroacetic acid was replaced with hydrochloric acid to obtain 4.2 mg (30%) of 1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-N-methyl-1H-imidazo[4,5-c]pyridine-4-carboxamidine hydrochloride (Table 1, Compound No. 94)

[0498]

^{1}H-NMR (270 MHz, DMSO-d_6) δ(ppm): 3.20(3H,d,J=5.2 Hz), 7.63-7.8(6H,m), 8.05(1H,d,J=5.6 Hz), 8.13(1H,s), 8.68(1H,d,J=5.6 Hz), 9.16(1H,s), 9.68(1H,s), 9.73(1H,s), 9.86(1H,s), 9.89(1H,s)

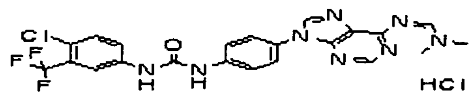
ESI (LC-MS positive mode) m/z 457 (M+H)

[Example 95]

N′-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-N,N-dimethylformamidine hydrochloride (Table 1, Compound No. 95)

[0499]

[Formula 137]



[0500]

In 10 mL of pyridine, 463 mg (0.957 mmol) of 1-[4-(6-amino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoro-methyl)phenyl)urea hydrochloride was dissolved, and 455 mg (3.83 mmol) of dimethylformamide dimethylacetal was added thereto and the mixture solution was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure, and then the residue was triturated with ethyl acetate and collected by filtration, and vacuum dried. The white solid was dissolved in 10 mL of methanol and 4N hydrochloric acid and concentrated under reduced pressure. The residue was triturated with ethyl acetate, collected by filtration, and then vacuum dried to obtain 580 mg (quantitative) of N'-(9-{4-[3-(4-chloro-3-(tri-fluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)-N,N-dimethylformamidine hydrochloride (Table 1, Compound No. 95) as a white solid.

[0501]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.30(3H,s), 3.45(3H,s), 4.30(1H,br.s), 7.60-7.80 (6H,q, J=7.2 Hz), 8.14(1H,m), 8.75(1H,s), 9.02(1H,s), 9.63(1H,s), 10.09(1H,s), 10.83(1H,s)

ESI (LC-MS positive mode) m/z 503 (M+H)

[Example 96]

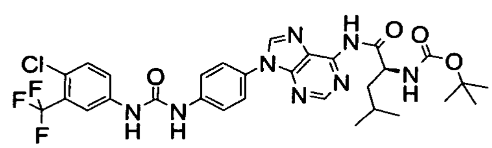
(S)-2-Amino-4-methyl-pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 96)

Step A

Preparation of [1-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-ylcarbonyl)-3-methylbutyl]carbamic acid tert-butyl ester

[0502]

[Formula 138]



[0503]

In 15 ml of tetrahydrofuran, 300 mg (0.620 mmol) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride was dissolved, and 771 mg (3.10 mmol) of tert-butoxycarbonyl-L-leucine, 1.60 g (3.10 mmol) of (benzotriazolyloxy)tripyrrolidino-phosphonium hexa-fluorophosphate (PyBOP) and 0.54 mL (3.10 mmol) of Hunig's base were added thereto and the mixture solution was stirred at room temperature for three days. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water. The organic phase was washed with a saturated sodium chloride solution, dried, and then concentated under reduced pressure. The residue was purified by Megabond Elute Silica Gel (10 g, ethyl acetate), to obtain 320 mg

(78%) of [1-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl) ureido]phenyl}-9H-purin-6-ylcarbonyl)-3-methyl-butyl]carbamic acid tert-butyl ester as a white solid.

[0504]

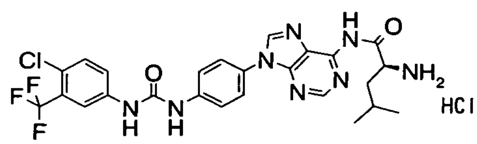
ESI (LC-MS positive mode) m/z 661 (M+H)

Step B

Preparation of (S)-2-amino-4-methyl-pentanoic acid (9-{4-[3-(4-chloro-3-(tirfluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 96)

[0505]

[Formula 139]



[0506]

In 5 mL of a 4N hydrogen chloride ethyl acetate solution, 310 mg (0.47 mmol) of [1-(9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-ylcarbonyl)-3-methylbutyl]carbamic acid tert-butyl ester was dissolved and the solution was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and the residue was triturated with ethyl acetate, collected by filtration, and then vacuum dried to obtain 280 mg (quantitative) of (S)-2-amino-4-methyl-pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 96).

[0507]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.90(3H,d,J=4.6 Hz), 0.96(3H,d,J=4.0 Hz), 1.60-1.65(1H,m), 1.70-1.80(2H,m), 4.40(1H, br.s), 7.65-7.83(6H,m), 8.14(1H,d,J=2.3 Hz), 8.30-8.37(3H,m), 8.75(1H,s), 8.93(1H,br.s), 9.38(1H,br.s), 9.55(1H,br.s)

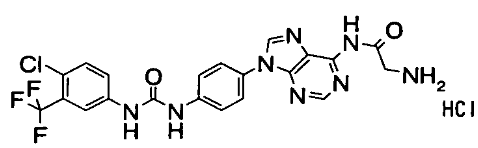
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 97]

2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)acetamide hydrochloride (Table 1, Compound No. 97)

[0508]

[Formula 140]



[0509]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-glycine by using the same method as in Example 96.

[0510]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.17(2H,m), 7.65-7.84(6H,m), 8.14(1H,d,J=2.0 Hz), 8.20-8.25(3H,m), 8.75(1H,s), 8.92(1H,s)

ESI (LC-MS positive mode) m/z 505 (M+H)

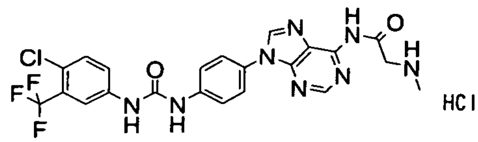
[Example 98]

N-(9-{4-[3-(4-Chloro-3-(triofluoromethyl)phenyl)-

ureido]phenyl}-9H-purin-6-yl)-2-methylaminoacetamide hydrochloride (Table 1, Compound No. 98)

[0511]

[Formula 141]



[0512]

The titled compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-sarcosine by using the same method as in Example 96.

[0513]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.30(3H,br.s), 4.87(2H, br.s), 7.65-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.87(1H,s), 8.93(1H,s), 9.48(1H,br.s), 9.53(1H,br.s), 9.67(1H,br.s)

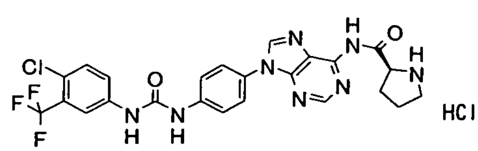
ESI (LC-MS positive mode) m/z 519 (M+H)

[Example 99]

(S)-Pyrrolidine-2-carboxylic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, compound No. 99)

[0514]

[Formula 142]



[0515]

The title compound can be synthesized from 1-[4-(6-

aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-proline by using the same method as in Example 96.

[0516]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.53-2.58(2H,m),2.62-2.68(2H,m), 3.83-3.85(1H,m), 4.34-4.36(2H,m), 7.64-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.77(1H,s), 8.93(1H,s), 8.95(1H,br.s), 9.55(1H,br.s), 9.77(1H,br.s)

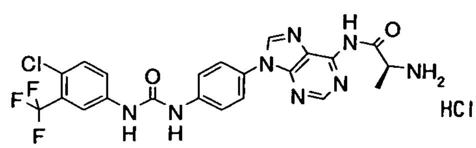
ESI (LC-MS positive mode) m/z 545 (M+H)

[Example 100]

(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl-phenyl)ureido]phenyl}-9H-purin-6-yl)propionamide hydrochloride (Table 1, Compound No. 100)

[0517]

[Formula 143]



[0518]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-alanine by using the same method as in Example 96.

[0519]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.54(3H,d,J=6.9 Hz), 4.4(1H,br.s), 7.65-7.83(6H,m), 8.14(1H,d,J=2.3 Hz), 8.30-8.37(3H,m), 8.79(1H,s), 8.93(1H,s), 8.95(1H,br.s), 9.52(1H,br.s), 9.72(1H,br.s)

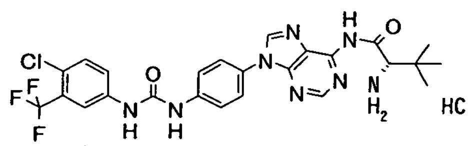
ESI (LC-MS positive mode) m/z 519 (M+H)

[Example 101]

(S)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3,3-dimethyl-butylamide hydrochloride (Table 1, Compound No. 101)

[0520]

[Formula 144]



[0521]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-choro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-tert-butylglycine by using the same method as in Example 96.

[0522]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.00(9H,s), 4.40(1H,br.s), 7.65-7.80(6H,m), 8.14(1H,d,J=2.0 Hz), 8.30-8.37(3H,m), 8.80(1H,s), 8.92(1H,s)

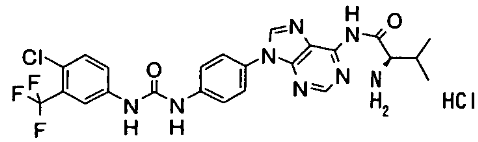
ESI (LC-MS positive mode) m/z 561 (M+H)

[Example 102]

(R)-2-Amino-N-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)-3-methylbutyl-amide hydrochloride (Table 1, Compound No. 102)

[0523]

[Formula 145]



[0524]

The titled compound can be synthesized from 1-[4-(6-amino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-D-valine by using the same method as in Example 96.

[0525]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.07(3H,d,J=6.9 Hz), 1.13(3H,d,J=6.9 Hz), 2.30-2.35(1H,m), 4.15-4.20(1H,m), 7.66-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.30-8.40(3H,m), 8.79(1H,s), 8.92(1H,s), 9.51(1H,br.s), 9.70(1H,br.s), 11.48(1H,br.s)

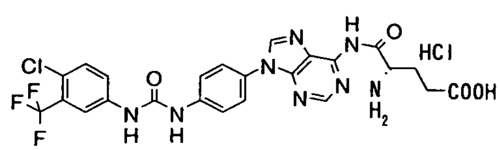
ESI (LC-MS positive mode) m/z 547 (M+H)

[Example 103]

(S)-4-Amino-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride (Table 1, Compound No. 103)

[0526]

[Formula 146]



[0527]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-

glutamic acid 5-tert-butyl ester by using the same method as in Example 96.

[0528]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.53-2.58(2H,m), 2.62-2.68(2H,m), 3.83-3.85(1H,m), 4.34-4.36(2H,m), 7.64-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.79(1H,s), 8.92(1H,s), 9.33(1H,br.s), 9.47(1H.br.s)

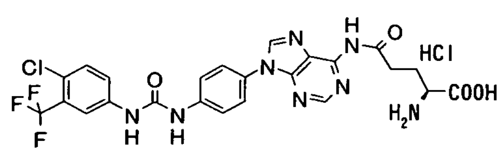
ESI (LC-MS positive mode) m/z 577 (M+H)

[Example 104]

(S)-2-Amino-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-ylcarbamoyl)butanoic acid hydrochloride (Table 1, Compound No. 104)

[0529]

[Formula 147]



[0530]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-clhoro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-glutamic acid 1-tert-butyl ester by using the same method as in Example 96.

[0531]

ESI (LC-MS positive mode) m/z 577 (M+H)

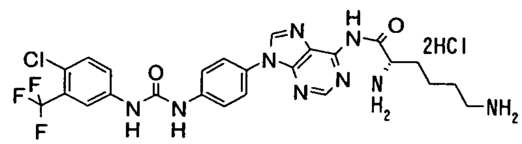
[Example 105]

(S)-2,6-Diaminohexanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-

yl)amide hydrochloride (Table 1, Compound No. 105)

[0532]

[Formula 148]



[0533]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and tert-butoxycarbonyl-L-lysine by using the same method as in Example 96.

[0534]

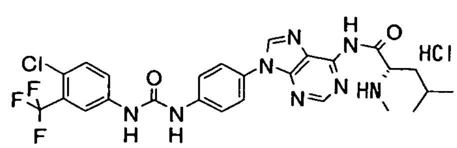
ESI (LC-MS positive mode) m/z 575 (M+H)

[Example 106]

(S)-4-Methyl-2-(methylamino)pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide hydrochloride (Table 1, Compound No. 106)

[0535]

[Formula 149]



[0536]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and N-methyl-tert-butoxy-carbonyl-L-leucine by using the same method as in

Example 96.

[0537]

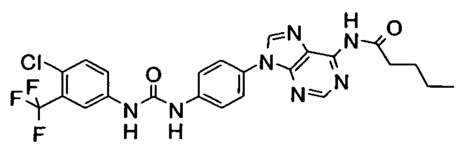
ESI (LC-MS positive mode) m/z 575 (M+H)

[Example 107]

Pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide (Table 1, Compound No. 107)

[0538]

[Formula 150]



[0539]

In 3 mL of pyridine, 30 mg (0.062 mmol) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride was dissolved, and 35 mg (0.186 mmol) of valeric anhydride and 8 mg (0.062 mmol) of 4-(N,N-dimethylamino)pyridine were added thereto, and the mixture solution was stirred at room temperature for 14 hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution, dried and concentrated. The residues was purified by Megabond Elute Silica Gel (1 g, ethyl acetate) to obtain 22.2 mg (56%) of pentanoic acid (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)amide (Table 1, Compound No. 107) as a white solid.

[0540]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.93(3H,t,J=7.0 Hz), 1.37(2H,m), 1.61(2H,m), 2.59(2H,m), 7.64-7.83(6H,m), 8.14(1H,d,J=2.3 Hz), 8.68(1H,s), 8.83(1H,s), 9.16(1H,s), 9.27(1H,br.s), 10.73(1H.br.s)

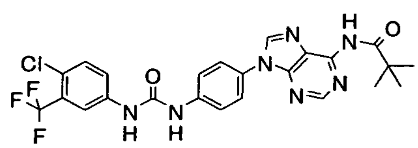
ESI (LC-MS positive mode) m/z 532 (M+H)

[Example 108]

N-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-2,2-dimethyl)-propionamide (Table 1, Compound No. 108)

[0541]

[Formula 151]



[0542]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and pivalic andhydride by using the same method as in Example 107.

[0543]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.30(9H,s), 7.60-7.82(6H,m), 8.14(1H,d,J=2.3 Hz), 8.76(1H,s), 8.81(1H,s), 9.17(1H,s), 9.28(1H,s), 10.24(1H,br.s) ESI (LC-MS positive mode) m/z 532 (M+H)

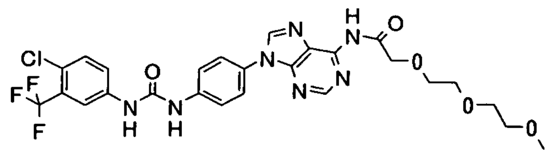
[Example 109]

N-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-2-[2-(2-methoxy)-

ethoxy]acetamide (Table 1, Compound No. 109)

[0544]

[Formula 152]



[0545]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and 2-[2-(2-methoxyethoxy)-ethoxy]acetyl chloride by using the same method as in Example 107.

[0546]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.20(2H,s), 3.41-3.45(2H,m), 3.55-3.65(4H,m), 4.69-4.75(2H,m), 4.37(3H,s), 7.64-7.84(6H,m), 8.14(1H,d,J=2.3 Hz), 8.73(1H,s), 8.88(1H,s), 9.25(1H,br.s), 9.39(1H,br.s), 10.45(1H,br.s)

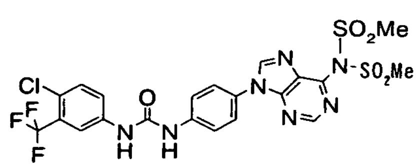
ESI (LC-MS positive mode) m/z 608 (M+H)

[Example 110]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(di-methanesulfonylamino)-purin-9-yl]phenyl}urea (Table 1, Compound No. 110)

[0547]

[Formula 153]



[0548]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and methanesulfonyl chloride by using the same method as in Example 107.

[0549]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.93(6H,s), 7.62-7.91(6H,m), 8.14(1H,br.s), 8.40(1H,t,J=7.9 Hz), 8.83-8.86(2H,m), 9.05(1H, s), 9.16(1H, s), 9.32(1H,br.s), 9.45(1H,br.s)

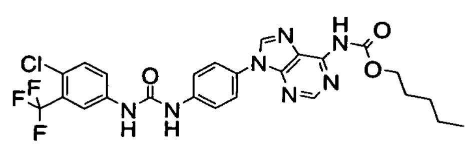
ESI (LC-MS positive mode) m/z 604 (M+H)

[Example 111]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid pentyl ester (Table 1, Compound No. 111)

[0550]

[Formula 154]



[0551]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and pentyl chloroformate by using the same method as in Example 107.

[0552]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.90(3H,t,J=6.9 Hz), 1.32-1.36(4H,m), 1.66(2H,dd,J=6.6, 7.3 Hz), 4.14(2H,t,J=6.6 Hz), 7.60-7.80(6H,m), 8.16(1H,d,J=2.7

Hz), 8.67(1H, s), 8.81(1H,s), 9.38(1H,br.s), 9.49(1H,br.s), 10.58(1H,br.s)

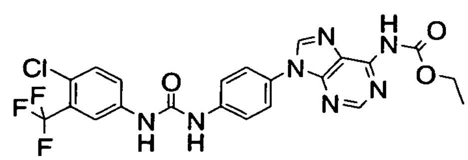
ESI (LC-MS positive mode) m/z 562 (M+H)

[Example 112]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid ethyl ester (Table 1, Compound No. 112)

[0553]

[Formula 155]



[0554]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and ethyl chloroformate by using the same method as in Example 107.

[0555]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.28(3H,t,J=6.9 Hz), 4.19(2H,t,J=6.9 Hz), 7.62-7.82(6H,m), 8.15(1H,d,J=2.3 Hz), 8.68(1H,s), 8.82(1H,s), 9.32(1H,br.s), 9.45(1H,br.s), 10.58(1H,br.s)

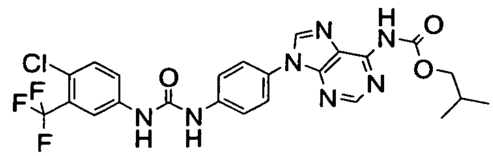
ESI (LC-MS positive mode) m/z 520 (M+H)

[Example 113]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid isobutyl ester (Table 1, Compound No. 113)

[0556]

[Formula 156]



[0557]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and pentyl chloroformate by using the same method as in Example 107.

[0558]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.97(6H,d,J=6.6 Hz), 1.95(1H,m), 3.95(2H,d,J=6.6 Hz), 7.62-7.82(6H,m), 8.18(1H,br.s), 8.67(1H,s), 8.80(1H,s), 9.17(1H,br.s), 9.29(1H,br.s)

ESI (LC-MS positive mode) m/z 548 (M+H)

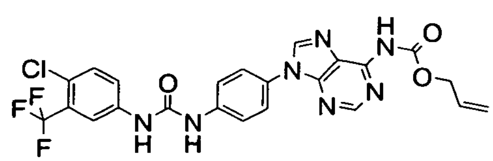
[Example 114]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid allyl ester

(Table 1, Compound No. 114)

[0559]

[Formula 157]



[0560]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and allyl chloroformate by using

the same method as in Example 107.

[0561]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.69(2H,d,J=5.3 Hz), 5.27(1H,dd,J=2.0, 10.5 Hz), 5.44(1H,dd,J=2.0, 15.5 Hz), 6.00(1H,m), 7.62-7.82(6H,m), 8.17(1H,d,J=2.3 Hz), 8.68(1H,s), 8.83(1H,s), 9.49(1H,br.s), 9.60(1H,br.s, 10.84(1H,br.s)

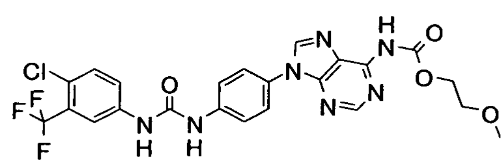
ESI (LC-MS positive mode) m/z 532 (M+H)

[Example 115]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid 2-methoxyethyl ester (Table 1, Compound No. 115)

[0562]

[Formula 158]



[0563]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and 2-methoxyethyl chloroformate by using the same method as in Example 107.

[0564]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.29(3H,s), 3.60(1H,d,J=4.6 Hz), 4.28(2H,d,J=4.6 Hz), 7.62-7.82(6H,m), 8.13(1H,d,J=2.0 Hz), 8.68(1H,s), 8.80(1H,s), 9.15(1H,br.s), 9.25(1H,br.s), 10.78(1H,br.s)

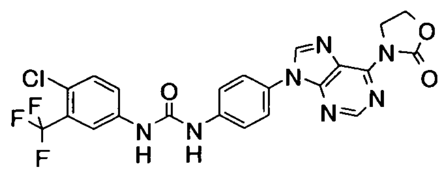
ESI (LC-MS positive mode) m/z 550 (M+H)

[Example 116]

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-{4-[6-(2-oxo-oxazolidin-3-yl)purin-9-yl]phenyl}urea (Table 1, Compound No. 116)

[0565]

[Formula 159]



[0566]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and 2-chloroethyl chloroformate by using the same method as in Example 107.

[0567]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.90(2H,t,J=5.3 Hz), 4.43(2H,t,J=5.3 Hz), 7.62-7.82(6H,m), 8.14(1H,d,J=2.0 Hz), 8.69(1H,s), 8.83(1H,s), 9.17(1H,br.s), 9.29(1H,br.s)

ESI (LC-MS positive mode) m/z 518 (M+H)

[Example 117]

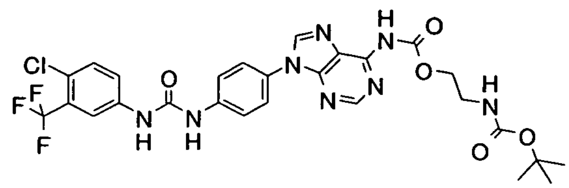
(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid 2-(methylamino)-ethyl ester hydrochloride (Table 1, Compound No. 117)

Step A

Preparation of (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl]carbamic acid 2-(tert-butoxycarbonylamino)ethyl ester

[0568]

[Formula 160]



[0569]

In 3 mL of methylene chloride, 110 mg (0.62 mmol) of (2-hydroxyethyl)-methylcarbamic acid tert-butyl ester and 108 μL (0.62 mol) of Hunig'a base were dissolved, and 74 mg (0.248 mmol) of triphosgene was added thereto at one time, and the mixture solution was stirred for 15 minutes. To the obtained solution, a solution obtained by dissolving 30 mg (0.062 mmol) of 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)phenyl)urea hydrochloride in 3 mL of pyridine was added and the mixture solution was stirred at room temperature for three hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution, dried and concentrated. The residue was purified by Megabond Elute Silica Gel (1 g, methanol:ethyl acetate=1:30) to obtain 13 mg (33%) of (9-{4-[3-(4-chloro-3-(trifluoro-methyl)phenyl)ureido]phenyl}-9H-purin-6-yl]carbamic acid 2-(tert-butoxycarbonylamino)ethyl ester as a white solid.

[0570]

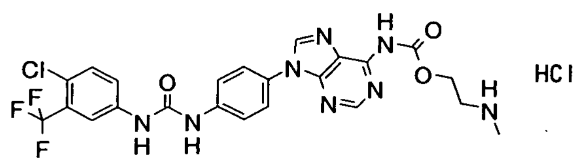
ESI (LC-MS positive mode) m/z 649 (M+H)

Step B

Preparation of (9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)carbamic acid 2-(methylamino)ethyl ester hydrochloride (Table 1, Compound No. 117)

[0571]

[Formula 161]



[0572]

In 2 mL of a 4N hydrogen chloride ethyl acetate solution, 13 mg (0.02 mmol) of (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl]carbamic acid 2-(tert-butoxycarbonylamino)ethyl ester was dissolved and the solution was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and then the residue was triturated with n-hexane:ethyl acetate=1:1, collected by filtration and vacuum dried to obtain 1.7 mg (16%) of (9-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl-carbamic acid 2-(methylamino)ethyl ester hydrochloride as a white solid.

[0573]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.85(3H,br.s), 4.37(2H,t,J=5.3 Hz), 7.62-7.81(6H,m), 8.08(1H.br.s), 8.14(1H,s), 8.71(1H,s), 8.88(1H,s), 9.60(1H,br.s), 9.82(1H,br.s)

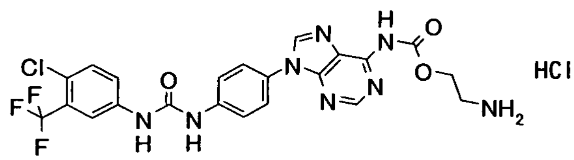
ESI (LC-MS positive mode) m/z 549 (M+H)

[Example 118]

(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]-phenyl}-9H-purin-6-yl]carbamic acid 2-aminoethyl ester hydrochloride (Table 1, Compound No. 118)

[0574]

[Formula 162]



[0575]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and (2-hydroxyethyl)carbamic acid tert-butyl ester by using the same techniques as in Example 117.

[0576]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.19(2H,m), 3.85(3H,br.s), 4.37(2H,t,J=5.3 Hz), 7.62-7.81(6H,m), 8.08(1H,.br.s), 8.14(1H,s), 8.71(1H,s), 8.88(1H,s), 9.60(1H,br.s), 9.82(1H,br.s)

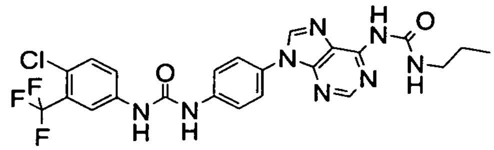
ESI (LC-MS positive mode) m/z 535 (M+H)

[Example 119]

1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl) ureido]phenyl}-9H-purin-6-yl)-3-propylurea (Table 1, Compound No. 119)

[0577]

[Formula 163]



[0578]

In 10 mL of pyridine, 300 mg (0.62 mmol) of 1-[4-(6-amino-purin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride was dissolved, and 1.58 g (18.6 mmol) of propyl isocyanate was added thereto and the mixture solution was stirred at 50°C for eight hours. The reaction solution was concentrated under reduced pressure, and then the residue was distributed between ethyl acetate and water, and the organic layer was washed with a saturated sodium chloride solution, dried and concentrated. The residue was triturated with n-hexane:ethyl acetate=1:1, collected by filtration and vacuum dried to obtain 210 mg (64%) of 1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido]phenyl}-9H-purin-6-yl)-3-propylurea (Table 1, Compound No. 119) as a white solid.

[0579]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.96(3H,t,J=7.2 Hz), 1.56(2H,q,J=7.3 Hz), 3.25(2H,m), 7.62-7.79(6H,m), 8.16(1H,d,J=2.3 Hz), 8.59(1H,s), 8.79(1H,s), 9.45(1H,br.s), 9.59(1H,br.s), 9.68(1H,br.s), 9.72(1H,br.s)

ESI (LC-MS positive mode) m/z 533 (M+H)

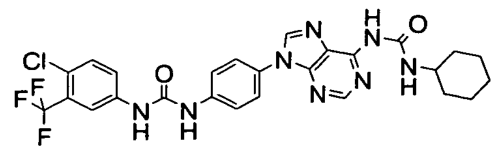
[Example 120]

1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-

ureido]phenyl}-9H-purin-6-yl)-3-cyclohexylurea (Table 1, Compound No. 120)

[0580]

[Formula 164]



[0581]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and cyclohexyl isocyanate by using the same techniques as in Example 119.

[0582]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.35(6H,m), 1.70(2H,m), 1.90(2H,m), 3.67(1H,m), 7.65-7.83(6H,m), 8.13(1H,d,J=2.0 Hz), 8.59(1H,s), 8.79(1H,s), 9.16(1H,s), 9.26(1H,s), 9.47(1H,br.s), 9.61(1H,s)

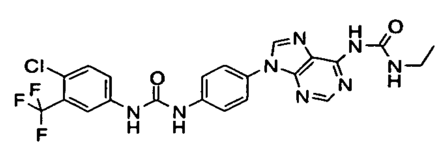
ESI (LC-MS positive mode) m/z 537 (M+H)

[Example 121]

1-(9-{4-[3-(4-Chloro-3-(trifluoromethyl)phenyl)-ureido]phenyl}-9H-purin-6-yl)-3-ethylurea (Table 1, Compound No. 121)

[0583]

[Formula 165]



[0584]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and ethyl isocyanate by using the same techniques as in Example 119.

[0585]

^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.17(3H,t,J=7.1 Hz), 3.30(2H,m), 7.62-7.80(6H,m), 8.13(1H,d,J=2.3 Hz), 8.59(1H,s), 8.79(1H,s), 9.15(1H,br.s), 9.26(1H,br.s), 9.39(1H,br.s), 9.66(1H,br.s)

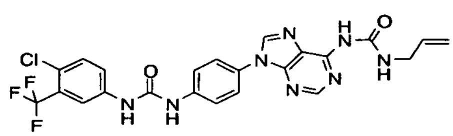
ESI (LC-MS positive mode) m/z 519 (M+H)

[Example 122]

1-Allyl-3-(9-{4-[3-(4-chloro-3-(trifluoromethyl)-phenyl)ureido]phenyl}-9H-purin-6-yl)urea (Table 1, Compound No. 122)

[0586]

[Formula 166]



[0587]

The title compound can be synthesized from 1-[4-(6-aminopurin-9-yl)phenyl]-3-(4-chloro-3-(trifluoromethyl)-phenyl)urea hydrochloride and allyl isocyanate by using the same techniques as in Example 119.

[0588]

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.95(2H,m), 5.13(3H,d,J=10.0 Hz), 5.24(1H,d,J=17.2 Hz), 6.95(1H,m), 7.62-7.80(6H,m), 8.12(1H,d,J=2.4 Hz), 8.59(1H,s),

8.79(1H,s), 9.15(1H,br.s), 9.25(1H,br.s), 9.55(1H,br.s), 9.78(1H,br.s)

ESI (LC-MS positive mode) m/z 531 (M+H)

[0589]

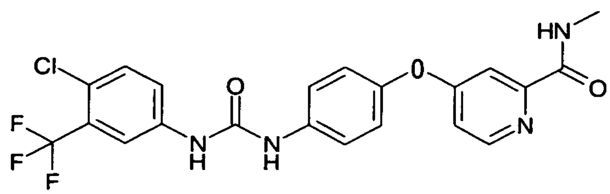
[Example B-1]

RAF-1 Enzyme Inhibition Test

With respect to the compounds relating to the present invention and the known compound (BAY 43-9006):

[0590]

[Formula 167]



the Raf-1 protein inhibition activity was measured. The enzymatic reaction was measured by incorporation of ^{33}P-phosphoric acid into MEK 1 protein by a recombinant Raf-1 protein. The activity was measured by preparing 50 μL of a reaction solution containing a dimethyl sulfoxide solution of the compound relating to the present invention or the compound BAY 43-9006 at a varied concentration [as the final concentration, the reaction solution containing 50 mL of TRIS hydrochloric buffer (pH 7.5), 1 mM of dithiothreitol, 100 mM of sodium chloride, 10 mM of potassium fluoride, 1 mM of sodium vanadate, 10 mM of magnesium chloride, 10 μM of adenosine triphosphate (ATP, containing ^{33}P-ATp of 12580Bq),2 μg of GST-MEK1 and 25 ng of an activated type GST-Raf-1]; keeping the reaction solution

at 30°C for 45 minutes; adding 100% trichloroacetic acid to the reaction solution in an amount twice the volume of the reaction solution to precipitate a proteinous component; recovering the precipitate on a glass filter; and measuring the radioactivity of the recovered product. The 50% inhibition concentration (IC_{50}) was obtained from the inhibition ratio to a sample-free reference.

[0591]

The compound BAT 43-9006 was prepared on the basis of the description (Example 41) of WO 00/42012. The results of measurement of Raf-1 inhibition activity are shown in Table 2.

[0592]

[Tanle 2]

Table 2

50% Enzyme Inhibition Concentration (IC_{50}value)/μM

Compound	Raf-1 Enzyme Inhibition
BAY43-9006	0.027
Compound 18	0.047
Compound 30	0.033
Compound 36	0.110
Compound 46	0.067
Compound 93	0.053
Compound 95	0.042
Compound 96	0.044
Compound 104	0.074
Compound 119	0.013

[0593]

As described in Table 2, the group of the compounds relating to the present invention has Raf-1 enzyme inhibition activity.

[Example B-2]

Cell Growth inhibition Test

With respect to the compounds relating to the present invention and the known compound (BAY 43-9006), cell growth inhibition activity was measured.

[0594]

A sample compound was in-series diluted with dimethyl sulfoxide, and then was 1/50 diluted with a Ca^{2+}- and Mg^{2+}-free phosphate-bufferized physiological saline and its 20 μL was poured to a 96-wel plate. Cell suspensions having 3,000 cells/180 μL were prepared with a culture medium obtained by adding 10% bovine fetal serum to McCoy's 5a medium in measuring the grow inhibition of human colorectal cancer cell strain HCT 116; a culture medium obtained by adding 10% bovine fetal serum, 30 μg/mL of vein endothelial cell growth auxiliary and 50 μg/mL of heparin to PRMI 1640 medium in measuring the grow inhibition of VEGF non-dependent human umbilical vein endothelial cells (HUVEC, purchased from Clonetics); and a culture medium obtained by adding 20 mg/mL of 10% bovine fetal serum and 20 ng/mL of VEGF to PRMI 1640 medium in measuring the grow inhibition of VEGF dependent HUVEC. Each of these cell suspensions was dividedly poured to the sample added plate in 180 μL/well and cultured in a 5% carbon dioxide incubator at 37°C. After 72 hours, 20 μL of WST-(HCT 116, a product of Dojin)

or WST-1 (HUVEC, a product of Roche diagnostics) was added thereto to each well and the absorbance at 450 nm (reference wavelength: 650 nm) was measured. From the growth inhibition ratio of addition of the sample compound to no-addition of the sample compound as a reference, the 50% growth inhibition IC_{50}) of the sample compound was calculated.

[0595]

With respect to the group of representative compounds of the present invention, the IC_{50} values of HCT 116 and HUVEC (VEGF nondependent growth and VEGF dependent growth) are shown in Table 3.

[0596]

[Table 3]

Table 3

50% Growth Inhibition Concentration (IC_{50}value)/μM

Compound	HUVEC (VEGF Nondependence)	HUVEC (VEGF Dependence)	HCT116
Bay43-9006	4.6	0.021	3.0
Compound 1	2.1	0.092	1.2
Compound 35	2.4	0.46	2.8
Compound 36	0.25	0.079	0.7
Compound 49	4.1	0.19	7.3
Compound 53	2.8	0.44	3.4
Compound 95	2.6	0.47	3.1
Compound 96	3.2	0.091	2.2
Compound 104	7.4	0.93	3.9
Compound 119	0.97	0.064	3.7

[0597]

As described in Table 3, the group of the compounds relating to the present invention has growth inhibition action on human colorectal caner strain HCT 116. Further, it has growth inhibition action on human umbilical vein endothelial cell (HUVEC).

[0598]

[Example B-3]

<u>Antitumor Test</u>

With respect to the compounds relating to the present invention and the known compound (BAY 43-9006), cell growth inhibition activity was measured.

A cell suspension of a human colorectal cancer cell strain HCT 116 was prepared with a Hunks' balanced salt solution. Its 5.0×10^6 were inoculated subcutaneously to the flank of each male Balb/c nude mouse. When the mean volume of a tumor reached 200 to 250 mm^3, a sample compound was orally administered one time a day for 5 days. The tumor volume was calculated from the calculation formula: $0.5 \times (\text{minor diameter})^2 \times (\text{major diameter})$, and the tumor growth inhibition ratio was calculated from the ratio of the tumor growth of the sample administered group to that of a reference group. The dosage in the antitumor test, the tumor growth inhibition ratio on the final administration day and the reduction in body weight on day 7 after starting administration are shown in Table 4.

[0599]

[Table 4]

Table 4 Antitumor Test

Compound	Dosage (mg/kg)	Tumor Inhibition Ratio (%)	Body Weight Reduction ratio (%)
Bay43-9006	100	83	17.0
Compound 36	200	81	5.9
Compound 93	200	79	6.0
Compound 119	200	89	8.5

[0600]

As described in Table 4, the group of the compounds relating to the present invention has antitumor activity and is safe with a small reduction in body weight.

[Example B-4]

[Method of Measuring Solubility to fasted state simulated intestinal fluid]

To a 96-well plate, 2 μL of a dimethyl sulfoxide solution of the compound relating to the present invention or that of the compound BAY 43-9006 was poured at one time, respectively, and fasted state simulated intestinal fluid (pH 6.5) was added 200 μL by 200 μL, and the plate was shaken at 37°C for 20 hours. The solution was filtered with a membrane filter and 101 μL of the filtrate was transferred to an UV plate, and 100 μL of a mixed solution of ethanol:water=2:1 was added thereto. On the other hand, as a standard solution, 2 μL of a dimethyl sulfoxide solution was added to a solution containing 4 μL of dimethyl sulfoxide, 400 μL of ethanol and 200 μL of water and the obtained solution was transferred 101 μL by 101 μL to the UV plate and to this UV plate, the simulated fasting

bile-containing intestinal juice (pH 6.5) was added 100 μL by 100 μL. The solubility was calculated by the following equation.

Solubility = (absorbance of sample solution-
blank)/(absorbance of standard solution-
blank)$\times$165 μL

wherein

165 μL is a concentration of the standard solution.

[Composition of fasted state simulated intestinal fluid]

Fasted state simulated intestinal fluid was prepared in accordance with E. Galia et al., Pharm. Res., 698, 1998.

[0601]

To about 90 mL of water, 161 mg of taurocholic acid, 59 mg of L-α-phosphatidylcholine, 0.39 g of potassium dihydrogenphosphate and 0.77 g of potassium chloride were added and the pH of the mixture solution was adjusted to 100 mL and the mixture solution was filtered with a membrane filter.

[0602]

The values relating to a representative group of the compounds of the present invention are shown in Table 5.

[0603]

Table 5

Solubility Test

Compound	Solubility (μg/mL)
BAY43-9006	10
Compound 21	24
Compound 34	34
Compound 35	24
Compound 36	22
Compound 92	76
Compound 96	102
Compound 109	39
Compound 115	19
Compound 119	39

[0604]

As described in Table 5, the group of the compounds relating to the present invention excels in the solubility in fasted state simulated intestinal fluid.

[Name of Document] Abstract

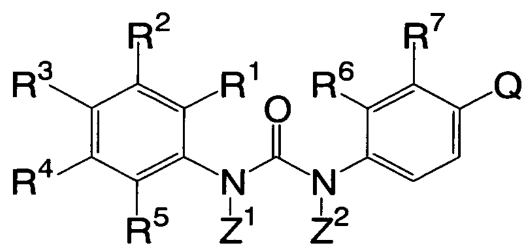
[Abstract]

[Problems] The present invention provides a compound useful as a preventive and therapeutic agent effective for diseases with phathologic angiogenesis.

[Measures of Solving the Problems]

According to the present invention, there is provided a compound represented by the formula (1):

[Formula 1]

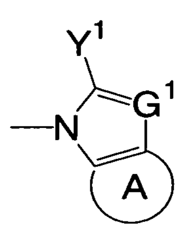


(1)

wherein

R^1, R^2, R^3, R^4 and R^5 are each independently selected from a hydrogen atom, a halogen atom, a halo C_1-C_6 alkyl group and a halo C_1-C_6 alkoxy group; R^6 and R^7 are each independently selected from a hydrogen atom and a halogen atom; Z^1 and Z^2 are each independently selected from a hydrogen atom, a hydroxyl group and $-O(CHR^{11})OC(=O)R^{12}$; Q is a group of the formula:

[Formula 2]



wherein G^1 is C-Y^2 or N; a ring A is a benzene ring or

a 5- to 6-membered unsaturated heterocycle; and the ring A may be substituted with one to three same or different substituents W;

a pharmaceutically acceptable salt thereof or a prodrug thereof.

[Selected Drawing] None.